SYNTHESIS AND CHARACTERIZATION OF MONONUCLEAR PLATINUM(II) COMPLEXES WITH SOME THIONE LIGANDS

BY

AHMED ZAINELABDEEN ABDALLA MUSTAFA

A Thesis Presented to the
DEANSHIP OF GRADUATE STUDIES

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
Requirements for the Degree of

MASTER OF SCIENCE

In

CHEMISTRY

May 2013

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN- 31261, SAUDI ARABIA

DEANSHIP OF GRADUATE STUDIES

This thesis, written by **AHMED ZAINELABDEEN ABDALLA MUSTAFA** under the direction his thesis advisor and approved by his thesis committee, has been presented and accepted by the Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE IN CHEMISTRY**

Dr. Anvarhusein A. Isab
(Advisor)

Dr. Abdullah J. Al-Hamdan
Department Chairman

Dr. Mohammed Wazeer
(Member)

Dr. Salam A. Zummo
Dean of Graduate Studies

Dr. Mohammed Fettouhi
(Member)

8/6/13
Date

This thesis is dedicated to my parents
for their love, endless support
and encouragement

ACKNOWLEDGMENTS

All praise and glory to almighty Allah, who gave me courage and patience to carry out this work. Peace and blessing of Allah be upon his last Prophet Muhammad.

I would like to express my gratitude to my supervisor Dr. Anvarhusein Isab, for the useful comments, remarks and engagement through the learning process of this master thesis. I am also grateful to other committee members, Dr. Mohammed Wazeer, for his suggestion and encouragements, Dr. Mohammed Fettouhi, for his constant help and guidance, he has been helping me out and supported me throughout the course of this work and on several other occasions. Acknowledgement is due to the King Fahd University of Petroleum & Minerals and the Department of Chemistry for supporting this research and providing me with necessary infrastructure and excellent research environment.

Furthermore, I would like to thank Mr. M. Bahauddin, and Mr. Monim-Ul-Mehboob for introducing me to the topic as well for the support on the way. A special gratitude I give to Mr. Mohammad Arab, and Mr. Mansour Al-Zaki, for their help through the NMR, IR and Raman spectroscopy. Special thanks to Mr. Khalid Hamid, for his help and support.

I also acknowledge my colleagues and friends, especially the whole Sudanese community with whom I had a pleasant, enjoyable and fruitful company.

I would like to express my deepest appreciation to all those who provided me the possibility to complete this work.

Finally, I extend my acknowledgement and heartfelt love to my parents, brothers and sisters, whom have been with me all the time to spur my spirits.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

(1) MeImt	:	R = CH_3, R$^{/}$ = H; N-methylimidazolidine-2-thione
(2) EtImt	:	R = C_2H_5, R$^{/}$ = H; N-ethylimidazolidine-2-thione
(3) PrImt	:	R = C_3H_7, R$^{/}$ = H; N-propylimidazolidine-2-thione
(4) *i*-PrImt	:	R = *i*-C_3H_7, R$^{/}$ = H; N-(*i*-propyl)imidazolidine-2-thione
(5) Me_2Imt	:	R = R$^{/}$ = CH_3; N,N$^{/}$-dimethylimidazolidine-2-thione
(6) Et_2Imt	:	R = R$^{/}$ = C_2H_5; N,N$^{/}$-diethylimidazolidine-2-thione
(7) *i*-Pr_2Imt	:	R = R$^{/}$ = *i*-C_3H_7; N,N$^{/}$-di-(*i*-propyl)imidazolidine-2-thione
(8) EtMeImt	:	R = C_2H_5, R$^{/}$ = CH_3; N-ethyl-N$^{/}$-methylimidazolidine-2-thione
(9) Diaz	:	R = H; 1,3-Diazinane-2-thione
(10) EtDiaz	:	R = C_2H_5; N-ethyl-1,3-Diazinane-2-thione
(11) Diap	:	1,3-Diazipane-2-thione
1A	:	$[Pt(MeImt)_2Cl_2]$
1B	:	$[Pt(MeImt)_4]Cl_2.2H_2O$
2A	:	$[Pt(EtImt)_2Cl_2]$
2B	:	$[Pt(EtImt)_4]Cl_2$
3A	:	$[Pt(PrImt)_2Cl_2]$
3B	:	$[Pt(PrImt)_4]Cl_2$
4A	:	$[Pt(i\text{-}PrImt)_2Cl_2]$
4B	:	$[Pt(i\text{-}PrImt)_4]Cl_2$

5A : $[Pt(Me_2Imt)_2Cl_2]$

6A : $[Pt(Et_2Imt)_2Cl_2]$

7A : $[Pt(i\text{-}Pr_2Imt)_2Cl_2]$

8A : $[Pt(EtMeImt)_2Cl_2]$

9A : $[Pt(Diaz)_2Cl_2\ ]$

9B : $[Pt(Diaz)_4]Cl_2.H2O$

10A : $[Pt(EtDiaz)_2Cl_2\ ]$

10B : $[Pt(EtDiaz)_4]Cl_2$

11A : $[Pt(Diap)_2Cl_2]$

11B : $[Pt(Diap)_4]Cl_2$

ABSTRACT

Full Name : [Ahmed Zainelabdeen Abdalla Mustafa]

Thesis Title : [Synthesis and Characterization of Mononuclear Platinum(II) Complexes With Some Thione Ligands]

Major Field : [Chemistry]

Date of Degree : [May 2013]

Despite the success of cisplatin in the treatment of individuals afflicted with advanced testicular cancer and other types of cancer, it has a broad spectrum of side-effects like nephrotoxicity and neurotoxicity. There is a need for new platinum complexes that are able to broaden the biological activity spectrum and eliminate the multifactorial drug resistance. Surprisingly, cisplatin based DNA-Pt adducts and its analogues are almost identical, leading to similar patterns of tumor sensitivity and susceptibility to resistance.

Platinum(II) complexes with sulfur-containing ligands have shown high efficacy for some human cell line comparable to that of the cisplatin. In this study, we synthesized a series of new platinum complexes with some thione ligands (Figure 1) and characterized them using elemental analysis, Infrared spectroscopy (IR), Raman spectroscopy, (^{1}H and ^{13}C solution NMR, as well as ^{13}C, ^{15}N and ^{195}Pt solid NMR spectroscopy) and single-crystal X-ray crystallography. The coordination site was discussed in the light of the various data obtained. Two of the complexes, $[Pt(MeImt)_4]Cl_2$ (**1B**) and $[Pt(Diaz)_4]Cl_2$ (**9B**), were characterized based on their X-ray crystallography and showed that the platinum atom is connected to four sulfur atoms; each belonging to thione ligand in a distorted square planar geometry.

ملخص الرسالة

الاسم الكامل: أحمد زين العابدين عبدالله مصطفى

عنوان الرسالة: تصنيع و توصيف معقدات البلاتين (II) احادية النواة مع بعض متصلات الثايون

التخصص: الكيمياء

تاريخ الدرجة العلمية: مايو 2013

على الرغم من نجاح عقار سيسبلاتين (cisplatin) في علاج الآلاف من المرضى المصابين بسرطان الخصية المتطورة وأنواع أخرى من السرطان، إلا أن لديه مجموعة واسعة من الآثار الجانبية مثل الفشل الكلوي والسمية العصبية (تلف الأعصاب) وغيرهما. هناك حاجة ماسة لتحضير معقدات بلاتين جديدة قادرة على توسيع نطاق النشاط البيولوجي والقضاء على مقاومة الخلايا للعقاقير. المثير للدهشة أن نواتج الاضافة المتكونة من تفاعل سيسبلاتين ونظائره مع الحمض النووي (DNA) تكاد تكون متطابقة، مما يؤدي إلى أنماط مماثلة من حساسية الورم و قابلية الخلايا السرطانية للمقاومة. لقد أظهرت معقدات البلاتين (II) التي تتكون من مترابطات تحتوي على الكبريت فعالية عالية بالنسبة لبعض خطوط الخلايا البشرية مقارنة بالسيسبلاتين. في هذه الدراسة، قمنا بتخليق سلسلة من معقدات البلاتين الجديدة مع بعض مترابطات الثيون (الشكل 1) ووصفناها بواسطة تقنيات تحليل العناصر (Elemental Analysis)، مطيافية الأشعة تحت الحمراء (Infrared spectroscopy)، مطيافية رامان (Raman spectroscopy)، الرنين النووي المغناطيسي (NMR)، و الأشعة السينية البلورات (X-ray crystallography). تم مناقشة موقع الترابط إعتمادا على النتائج المتحصل عليها ووجد أن جميع المترابطات تتصل مع الذرة المركزية عن طريق ذرة الكبريت فيها .أيضا تم دراسة إثنان من هذه المعقدات عن طريق الأشعة السينية للبلورات **(1B)** $[Pt(MeImt)_4]Cl_2$ و**(9B)** $[Pt(Diaz)_4]Cl_2$ ووجد أن ذرة البلاتين المركزية ترتبط مع أربع ذرات كبريت في أي من المركبات وتقع في مركز رباعي سطوح مشوه.

CHAPTER 1

INTRODUCTION

Since the discovery of platinum-based drug, cispatin [1] and finding its ability in the treatment of malignant tumors of the urogenital tract and some other types of cancers [2], platinum metal became one of the most important players in the field of bioinorganic chemistry. Despite the success of cisplatin in the treatment of thousands of individuals afflicted with advanced testicular cancer [3], ovarian carcinoma [4], head and neck cancer, melanoma, and lymphomas cancers [5], its clinical use diminished by its side effects such as nephrotoxicity [6] and gastrointestinal effects [7], and also by the resistance of cancer cells to the drug. Thousands of platinum complexes have been synthesized in order to overcome these side effects. It has been found that all platinum(II) complexes share one common structure which is *cis* coordination of two amino groups (bearing at least NH) and two leaving groups such as chloride, citrate or oxalate [8, 9], they bind to the DNA through 1,2-intrastrand cross-links, between N7 atoms of two adjacent Guanine (G) with platinum(II) ion [10], therefore, they cause in most cases same side effects.

The need for generation of new platinum complexes that are able to broaden the biological activity spectrum and eliminate the multifactorial drug resistance resulted in the formation of structurally novel platinum complexes containing biologically active ligands that are supposed to interact with the DNA following a mechanism different than

the one of cisplatin. Studies found that cisplatin-like drugs can introduce nephrotoxicity due to their reaction with sulfur-containing amino acids of the proteins; cysteine and methionine [10]. Platinum(II) complexes with sulfur-containing ligands, like dimethyl sulfoxide, dimethyl sulfide, xanthate and thiosemicarbazones [11-13], have represented high efficacy for some human cell line. Thiourea and its derivatives, as sulfur-containing ligands, may give better results if they coordinate with the platinum(II) ion. They have been used for a long time as antifungal agents [14], rescue agents against nephritic side effects during cispalin administration [10], and as inhibitors of HIV-1 and HIV-2 reverse transcriptases [15]. Platinum(II) complexes with thiourea ligands demonstrated that they can bind to the DNA in a different mechanism than that of cisplatin and showed excellent cytotoxicity against ovarian and leukemia cancer cell lines [16, 17]. This success of thiourea and its derivatives in cancer treatment encouraged us to synthesize new platinum complexes with some thiourea derivatives and characterize them using different analytical techniques.

1.1 Research problem

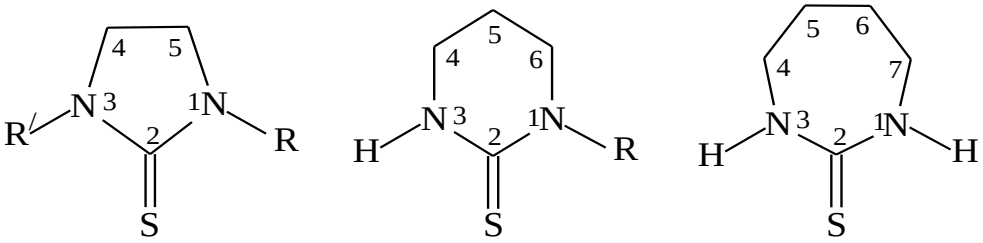
Cisplatin-like drugs can introduce nephrotoxicity due to their reaction with sulfur-containing nucleophile glutathione (γ-L-glutamyl-L-cysteinylglycine, GSH) [18]. In recent years, research has focused on the study of platinum complexes with sulfur-containing ligands. Those based on thiourea have long been known and their importance, at first, was not because of their biological activities. For instance, the tetra(thiourea)platinum(II) chloride's structure was determined in order to study the electronic effects of the ligand on the metal bonding [19]. Thiourea derivatives along

with platinum(II) complexes were also synthesized and crystallographically characterized because of the interest in new platinum anticancer complexes with heterocyclic ligands containing sulfur and nitrogen atom. As an example Tetrakis(1-methyl-2(3H)-imidazolinethione)platinum(II) chloride and nitrate, were synthesized in 1982 [20] and in 2004 [21], respectively.

This success of platinum complexes with S-donor ligands in cancer treatment encouraged us to prepare a series of thione-containing platinum(II) complexes.

1.2 Aims of the study

i. To study the reaction of K_2PtCl_4 with a series of thione ligands (Figure 1) in 1:2 & 1:4 ratios to synthesize complexes with general formulas $[PtL_2Cl_2]$ and $[PtL_4]Cl_2$, respectively.
ii. To fully characterize the synthesized complexes by elemental analysis, Infrared spectroscopy (IR), Raman spectroscopy, ^{1}H and ^{13}C solution NMR, as well as ^{13}C, ^{15}N and ^{195}Pt solid NMR spectroscopy and single-crystal X-ray crystallography.



(1-8) (9-10) (11)

1. R = CH_3, $R^{/}$ = H; N-methylimidazolidine-2-thione (MeImt)
2. R = C_2H_5, $R^{/}$ = H; N-ethylimidazolidine-2-thione (EtImt)
3. R = C_3H_7, $R^{/}$ = H; N-propylimidazolidine-2-thione (PrImt)
4. R = *i*-C_3H_7, $R^{/}$ = H; N-(*i*-propyl)imidazolidine-2-thione (*i*-PrImt)
5. R = $R^{/}$ = CH_3; N,$N^{/}$-dimethylimidazolidine-2-thione (Me_2Imt)
6. R = $R^{/}$ = C_2H_5; N,$N^{/}$-diethylimidazolidine-2-thione (Et_2Imt)
7. R = $R^{/}$ = *i*-C_3H_7; N,$N^{/}$-di-(*i*-propyl)imidazolidine-2-thione (*i*-Pr_2Imt)
8. R = C_2H_5, $R^{/}$ = CH_3; N-ethyl-$N^{/}$-methylimidazolidine-2-thione (EtMeImt)
9. R = H; 1,3-Diazinane-2-thione (Diaz)
10. R = C_2H_5; N-ethyl-1,3-Diazinane-2-thione (EtDiaz)
11. 1,3-Diazipane-2-thione (Diap)

Figure 1. Structures of different thione ligands

CHAPTER 2

LITERATURE REVIEW

2.1 Metals in Medicine – A Historical Background

The introduction of inorganic metals in medicine started thousands of years ago; since the time of the ancient Egyptians. Alums and Copper sulfate have been used due to their effects on the concoction produced in the process of potion preparation. Mercury was used recently, for the treatment of syphilis during the European epidemic between the 15th and 16th centuries [22]. The arsenic compound Salvarsan, has been introduced by Erlich in 1909 as a cure for syphilis too [23]. In the middle of the last century, two elements have changed the course of medicine by their great prominence in the medicinal use of metal compounds; one of these was the technetium, and the other was the platinum metal. The man-made element technetium, was discovered by C. Perrier and E. Serge in 1937, by neutron capture in molybdenum ores. During the latter part of the past century, technetium gained much interest because of its important contribution to the diagnostic medicine [24]. The use of platinum complexes in medicine, as an anticancer drug, started at the time of the great serendipitous discovery made by physicist-turned-biophysicist Barnett Rosenberg at Michigan State University, East Lansing, United States. He was trying to find whether there is a contribution of magnetic or electronic dipole fields on cell division by applying electromagnetic radiation on mammalian and bacterial cells. Inadvertently, a set of platinum electrodes was used in the growth chamber of

Escherichia coli. After applying the electromagnetic field, they were strange growth of the bacteria length; which reached up to 300 times the normal. This phenomenon could not be attributed to the effect of the applied field. Investigation studies found that the products of electrolysis process at the platinum electrodes (cisplatin, neutral *cis*-$[Pt(NH_3)_2Cl_2]$, and its platinum(IV) analogue, *cis*-$[Pt(NH_3)_2Cl_4]$), are the causing molecules of these biological effects [1]. At present, cisplatin is considered to be one of the most extensively used drugs against cancer. This is due to its activity against bladder, cervical, ovarian, head and neck, testicular, and small-cell and non-small cell lung cancers [25, 26]. In spite of the above mentioned advantages, cisplatin is ineffective in other cancers e.g. leukemia, gastrointestinal, and renal cancers [27].

2.2 Cancer and Cancer Chemotherapy

The term cancer is used for a collection of diseases which are known to cause failure of the division, growth and spreads all over the body and lead to a malignant tumor that attacks and damages the neighboring tissues [28]. Also it may extend to other parts of the body through the metastasis process, which is responsible for about 90% of cancer deaths [28, 29]. Cancer is also responsible for more than 13% of all deaths worldwide [28, 30], and it remains a difficult disease to treat. The challenge now is to get a drug which capable of eradicating this dread disease permanently.

The abnormality of the genetic material is the normal cause of cancer for the affected cells. This happens in a multistep process that is called tumorigenesis, which is responsible for producing or tending to produce tumors. It may include large or small-scale changes in DNA sequences, amplifications, and these changes affect the chromatin

structure. In all cases, these mutations can induce dramatic effects on general nuclear activities, such as DNA repair and DNA replication, or on special activities such as the expression of key growth regulatory genes [31]. Cancer is not just a cell disease, it is also a tissue disease that interrupts the normal relationships between epithelial cells and their underlying stromal cells [32]. Cancer can be treated based on radiotherapy, surgery, and with systemic chemotherapy. Unfortunately, these treatments do not totally cure the patients, they may not give benefit at all, or just a prolonged survival [22]. The aim of these chemotherapeutic drugs is to kill malignant tumor cells through inhibiting their cellular division, but there are just a small number of subgroups that can benefit from the effective targeted therapies [33]. It is clear that the development of a cancer chemotherapy is a very difficult task to achieve [34]. One of the most difficult problems associated with cancer chemotherapy is the nonspecific toxicity due to the spread out of the drug throughout the body, which requites large dose of the pharmaceuticals to achieve high concentrations at a local tumor [35]. Drug resistance also represents another problem in cancer chemotherapy (see also Section 2.4.3), which could be defined as the ability of cancer cells to resist different drugs [36]. There are different ways by which cancer cells can evade the chemotherapy. This resistance exists against all kinds of drugs, even the newly applied ones. Therefore, it's necessary to circumvent drug resistance to improve the chemotherapy [37]. Finally, the major problem that is facing the development of a new anticancer chemotherapy is the big gap between the promising findings in preclinical *in vivo* and *in vitro* models and the real clinical results obtained in the complex therapeutic situation of cancer in patients [34].

2.3 Natural Products in Cancer Chemotherapy

Natural products and their derivatives play a highly significant role in the discovery and development of the cytotoxic anticancer agents. Around half of the currently used anticancer drugs are originally natural products, it has also been found that these natural products and their derivatives represent about 60% of the newly introduced chemical in this field in the 1981–2002 period [38]. Microorganisms, marine organisms, and plants are the main sources of anticancer agents in cancer chemotherapy [39]. Actinomycetes are categorized as microorganisms that produce natural products with antimicrobial and anti-tumor properties. Figure 1 shows the structures of some microbial anti-tumor agents. The microbial product (actinomycin D) has shown 90% survival rate against stage I or stage II Wilm's tumor [40]. Bleomycin is used for testis and Hodgkin's lymphoma tumors and squamous cell carcinomas. It is originally produced by *Streptoalloteichus hindustanus*. A bleomycin derivative, Blenoxane, is used against the head, neck and testicles tumors, skin and lymphomas carcinomas [41], and the pingyangmycin derivative has also been used in china since 1978 in cancer therapy [42]. A dramatic example that demonstrates the efficacy of the natural products is that used against metastatic testicular cancer, which lifted the rate of treatment from 5% in 1974 to 90% in 2002; due to the use of a triple combination of the plant compound etoposide, the microbial product bleomycin and the synthetic agent cisplatin [43]. Camptothecin is a monoterpene indole alkaloid used against colon cancer, it has remarkable activity against lung, uterine, and ovarian cancer. Camptothecin produced by certain angiosperm plants, and by the *Nathapodytes Foetida* plant too. Endophytic fungus, *Entrophospora infrequens* also

produces camptothecin with a yield higher than that of the chemical synthesis. Fungal fermentation gives promising solutions for pharmaceutical production [44, 45].

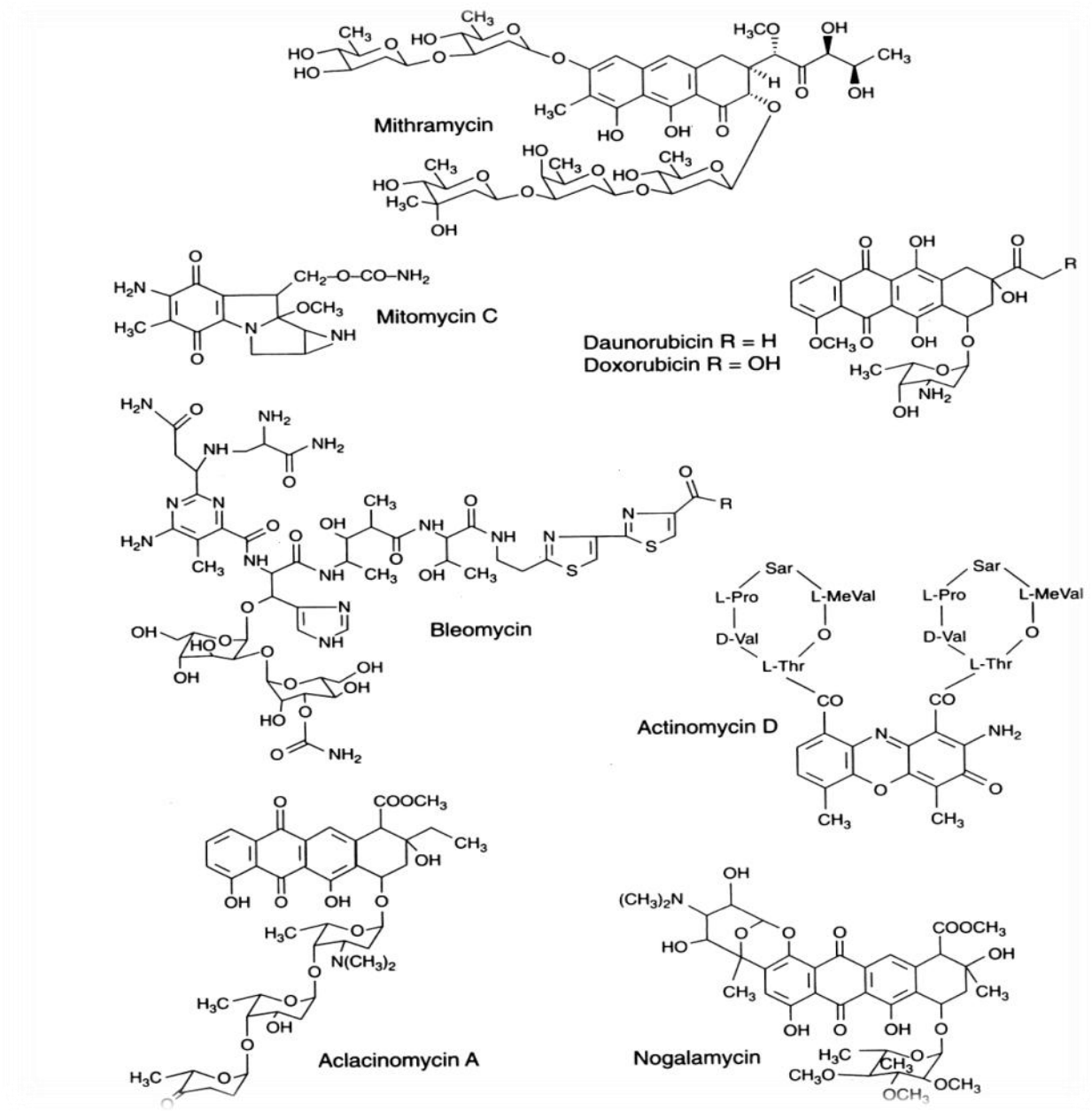


Figure 2. Structures of Some Microbial Anti-Tumor Agents

2.4 Cisplatin, *cis*-diamminedichloroplatinum(II) (CDDP)

This anticancer drug has been synthesized 130 years before its biological activity was discovered by Italian chemist Michele Peyrone in 1844, and was known as Peyrone's chloride [46]. Cisplatin was shown to cause marked tumor regression against the mice tumor, sarcoma-180 [47]. In 1971 the US National Cancer Institute (NCI) got the approval from the US president at that time, Richard M. Nixon, to begin testing the cytotoxicity of cisplatin against human cancer cell lines. The US Food and Drug Administration (FDA) approved in 1978 the use of cisplatin for the first time in association with other drugs in the treatment of metastatic ovarian cancer and metastatic testicular cancer [25]. The clinical use of cisplatin is diminished by drug resistance which can be either acquired or intrinsic. Many cancers, including ovarian cancer, that was initially treated with cisplatin gained resistant to it [25, 48]. Nephrotoxicity is one of the major toxicity limitations beside other side effects such as nausea and vomiting, myelotoxicity as well as peripheral neuropathy [6, 49]. Many attempts have been made in order to design new platinum drugs safer for patients, in particular, to remove or at least decrease the unpredictable and severe nephrotoxicity and/or to provide bioavailability for oral administration [50].

2.4.1 Platinum and Palladium Chemistry

The primary oxidation states of the platinum metal are II and IV, in special cases the I and III can be presented in cooperation with M−M bond, also it may be found in the 0 oxidation state, where CO, PR_3, and other π-acid ligands existed. Mixed oxidation states could be found, complexes usually having II and IV but some III. Pt(II) and Pd(II) found

in most of their complexes in square-planar geometry. Particularly the form complexes of general formula MX_2L_2, where X = monodentate anion; L = donor ligand. These complexes may exist as *cis* and *trans* isomers. Platinum and Palladium (II) commonly represent low affinity for hard ions such as O and F^-, and bind preferably to heavier halogens and ligands that can bind through the π system (ex., NO_2^-, CN^-, alkenes and alkynes). Although their complexes are usually similar, platinum complexes are more stable than their palladium analogues in both the kinetic and the thermodynamic sense. The kinetic inertness of platinum (II) complexes made them important in the field of coordination chemistry because of the ease of the study of the reaction mechanisms and the geometrical isomerization [51].

2.4.2 Cisplatin Mechanism of Action

There is overwhelming evidence that cisplatin becomes activated intracellularly before it can reach its target of DNA through the aquation mechanism (one of the chlorines is replaced by water) followed by formation of DNA adducts (Figure 3). Careful studies, conducted *in vitro* showed platinum binding to the N7 of the purine bases of DNA guanine (G), and to a lesser extent, adenine (A) to form different kind of platinum- DNA adducts, such as GpG 1,2 intrastrand (60–65% of all adducts) through binding of platinum complex to two adjacent guanine (G) of the same DNA strand, or ApG 1,2 intrastrand (20–25% of all adducts) through binding of platinum to two adjacent nucleobases; adenine (A) and guanine (G) of same DNA strand. There are also less frequent adducts which arise through binding to different DNA strands [52]. These adducts are the key to the success of the drug in programmed cell death (apoptosis) [50, 53].

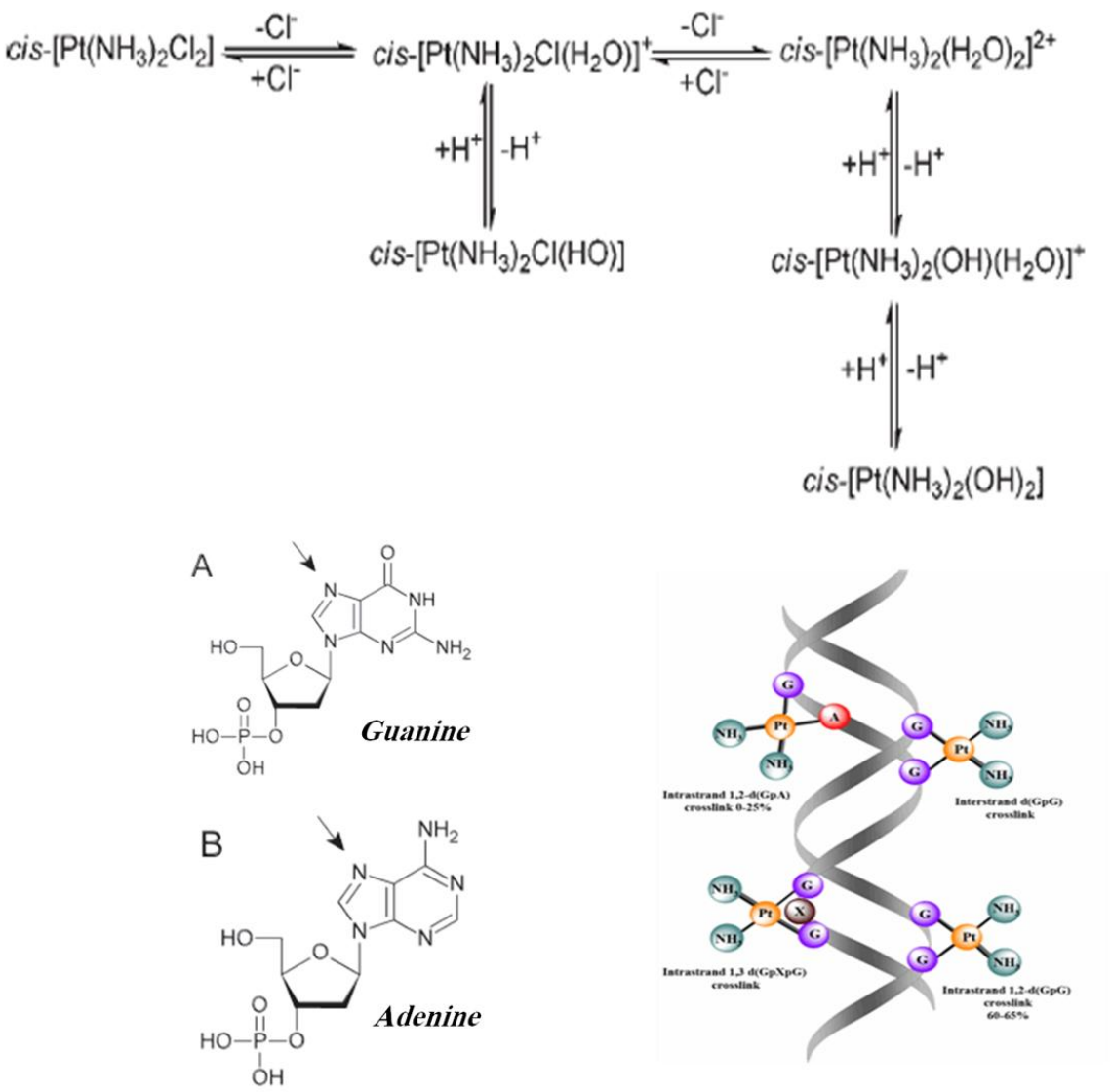


Figure 3. Cisplatin Mechanism of Action

2.4.3 Tumors Resistance to Cisplatin

Scientists were happy after the initial promising data obtained with cisplatin, and with its analogue carboplatin, then attention shifted to study of how tumor resistance was made during courses of chemotherapy with these anticancer drugs, and why some other tumors were essentially resistant. On the other hand, some studies were interested in the reason

behind the hypersensitivity of testicular cancer to cisplatin. The studies concluded that they may be two reasons behind the above mentioned tumor resistance: first is the failure in delivering an adequate quantity of the platinum drug to the DNA target, the second one is the failure to reach cell death after the formation of platinum-DNA adducts [50].

2.4.3.1.Resistance Through Insufficient DNA Binding

Over many years, it has been observed that, a resistance is acquired through the course of cisplatin administration in many tumor cells. A reduction of platinum concentration accumulated in the cells occurs compared to that of the parental cells [54]. However, till now, the exact mechanism in which the anticancer drug gets into the cells is still unclear. The intake of cisplatin is affected by several elements [55], like pH, the concentration of the potassium and the sodium ions, the existence of reducing agents; and the way that the drug is transportsed either through hypothesized gated channels or passive diffusion (Figure 4). The major plasma-membrane transporter, copper transporter-1 (CTR1), which has an essential role in copper homeostasis, was found to be involved in cisplatin influx, the loss of CTR1 has led to increase in drug resistance even high concentrations of cisplatin [56]. Also there is an evidence that the high concentration of sulfur-containing species, such as metallothioneins [57, 58], and glutathione [59, 60], which are affluent in the sulfur-containing amino acids, methionine and cysteine, will lead up to detoxification and thus causing resistance to cisplatin because platinum prefer to bind to sulfur.

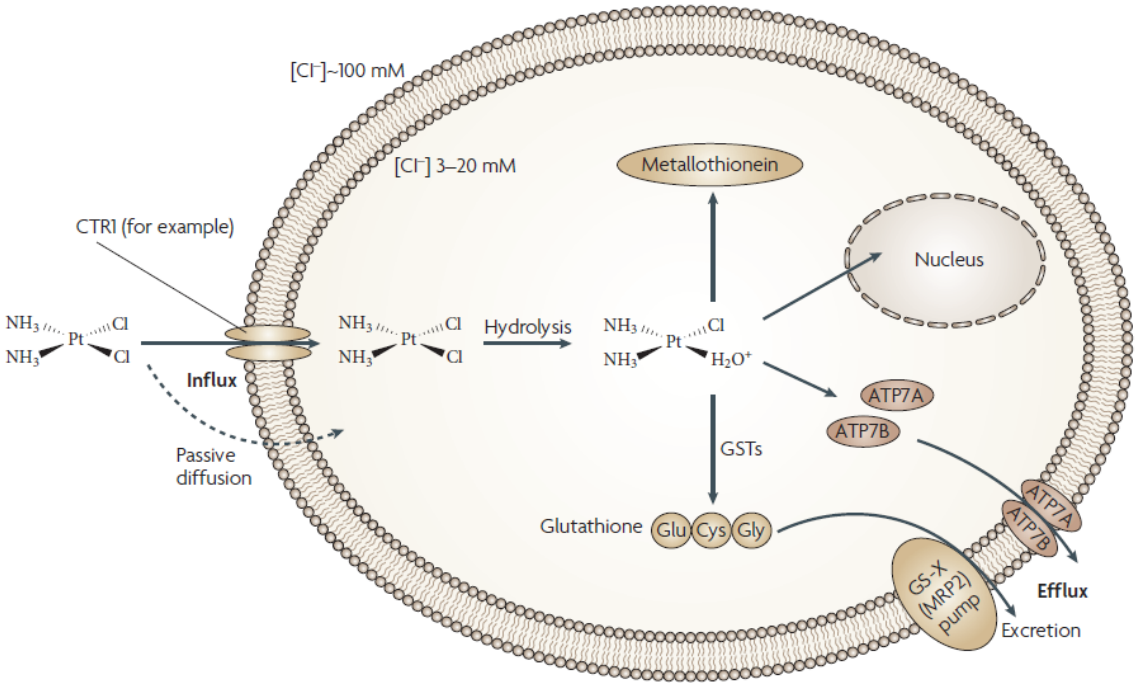


Figure 4. Tumor Resistance to Cisplatin Mediated by Inadequate Levels of Platinum Reaching Target DNA

2.4.3.2.Resistance mediated after DNA binding

Acquired resistance to cisplatin could also occur after the formation of platinum–DNA adducts, through cellular survival either by removal or tolerance of DNA damage [61]. The supersensitivity of testicular cancer to cisplatin was to be a result from DNA-repair deficiency. By contrast, there are many types of cisplatin-resistant cell lines have been shown to have tumor drug resistance because of the increase in the DNA-repair capacity [62].

2.4.4 Cisplatin Side Effects

The anti-tumor agent, cisplatin, is extremely used for solid tumors treatment, but it induces severe side-effects such as gastrointestinal toxicity, bone-marrow suppression,

ototoxicity, neuropathy, and nephrotoxicity; due to its lack of the selectivity for tumor cells. Nephrotoxicity is the main effect that hampers the use of cisplatin in the therapeutic process [63-65]. Studies found that 25% of patients may develop reversible azotemia after receiving a single dose of cisplatin [66]. In addition, irreversible kidney failure also may occur at large doses, or with frequent cycles of treatment [67]. Nephrotoxicity induced by a complex process involves severe cytotoxic effects on tubular epithelial cells, that reduce them via apoptosis, and necrosis, followed by fibroproliferative changes and inflammatory cell infiltration [68]. Cisplatin partially inhibits the protein synthesis in the tubular epithelial cells, and also disrupts the cellular antioxidant defense system (i.e., glutathione, GSH), resulting in DNA damage and lipid peroxidation. Glutathione, (GSH) could be administered to alter the nephrotoxicity induced by cisplatin [69], without affecting its antitumor activities [70].

2.5 Platinum Complexes as Anticancer Agents

Platinum compounds that are now excessively used in clinic represent a unique class of DNA damage [71]. It has been found that the only platinum complexes that possess *cis* geometry are able exhibit anticancer activity. The most active platinum complex, cisplatin, (Figure 5, A), was found to block the cell growth, while its *trans* isomer did not show such activity [71]. There are many platinum compounds that also inhibit the cell growth, these complexes generally bear at least one N-H group, that is needed because of its hydrogen-bond donor properties required in the binding with the biological target, or in the final structure. The general formula for the most known platinum antitumor complexes can be summarized in *cis*-$[PtX_2(NHR_2)_2]$, where the X =

leaving group, such as chloride, citrate or oxalate and R = organic fragment [72]. The development of platinum anticancer complexes resulted in what so called the second-generation platinum anticancer drug carboplatin [$Pt(C_6H_6O_4)(NH_3)_2$], (Figure 5, B), which has less side effects than cisplatin and is more readily applied in combination therapy. It has to be administered in a higher dosage because of its low reactivity. This anticancer agent is generally used for ovarian cancer therapy [71]. The third-generation drugs, oxaliplatin, (Figure 5, C), have been developed in order to overcome the spontaneous (intrinsic) drug resistance that may appear in particular tumors. These platinum complexes do not follow the classical *cis*-diamine structure with two leaving groups. Oxaliplatin is most effective in colon cancer therapy [73]. The Second-generation anticancer drugs such as (*cis*-diammine(1,1-cyclobutanedicarboxylato) platinum(II)), carboplatin, and [$PtCl_2$(dach)] (dach) *trans*-1,2- cyclohexanediamine) end up at the same DNA adducts like that of the parent drug cisplatin and so they are not expected to overcome the resistance of cells to the drug [74].

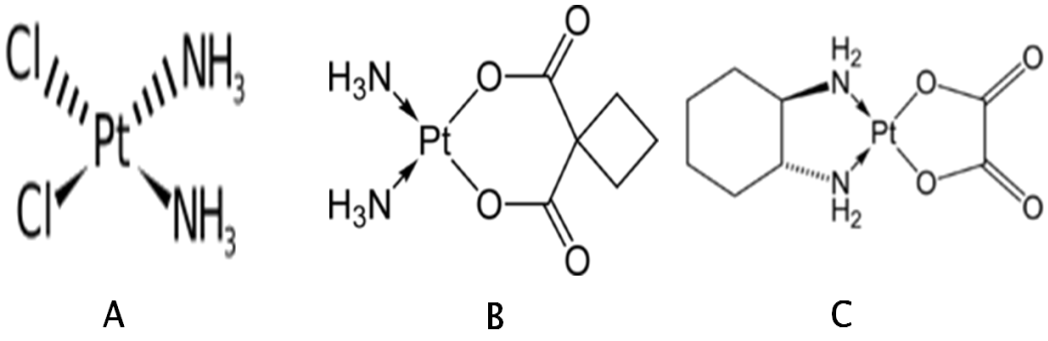


Figure 5. Chemical Structures of Platinum Compounds (A) Cisplatin, (B) Carboplatin and (C) Oxaliplatin

The need for generating new platinum complexes which are able to broaden the biological activity spectrum and lead to eliminate the multifactorial drug resistance, resulted in the formation of structurally novel platinum complexes containing biologically active ligands that are supposed to interact with the DNA in non-cisplatin behavior. Very careful investigation studies found that cisplatin-like drugs can introduce nephrotoxicity due to their reaction with sulfur-containing amino acids methionine and cysteine, because the platinum readily binds to sulfur [10]. The nephrotoxicity might be controlled by using rescue agents; usually sulfur-containing ligands these include thiourea, glutathione (GSH), sodium thiosulfate (STS), and Sodium Diethyldithiocarbamate (NaDDTC) [10, 75, 76]. Borch and Pleasants have suggested that nephrotoxicity might be a result of inactivation of specific enzymes due to binding with cisplatin through their sulfhyryl groups of cysteine residues and these rescue agents are able to restore the original structure of the enzymes by removing the platinum from their sulfur atoms, therefore reduce the nephrotoxicity [77]. Platinum(II) complexes with sulfur-containing ligands, such as dimethyl sulfoxide, dimethyl sulfide, xanthate and thiosemicarbazones have shown high efficacy for some human cell line comparable to that of the cisplatin [11-13]. Some platinum(II) complexes showed that they may induce apoptosis in a mechanism different than that of cisplatin and showed excellent cytotoxicity against leukemia and ovarian cancer cell lines [11, 17]. Thiourea and its derivatives, as a class of sulfur containing ligands, may give a better result if they coordinated with platinum(II) ion. They have been used for a long time as antifungal agents [14], rescue agent against nephritic side effects during cispalin administration [10], and as inhibitors of HIV-1 and HIV-2 reverse transcriptases [78].

2.6 Imidazolidine-2-thione and its N-substituted derivatives

1,3-imidazolidine-2-thiones and their derivatives are an interesting class of ligands due to their significant pharmaceutical benefits and their ambidentate nature [79]. Substituted Imidazolidine-2-thiones offer noticeable biological activity; for example, they have been reported to exhibit antimicrobial activity [80], antifungal activity , anti-HIV activity and in cancer treatment [81]. These ligands can coordinate to a metal through various chelating modes, by their sulfur or nitrogen atoms. Also they may exist in a thiol-thione equilibrium [82]. Studies found that the latter one is the dominant form of the complexes in the solid state and in the most common solvents [82, 83]. The reactions of thione ligands with transition metals have been well studied. Complexes of Cu(I), Ag(I), Pd(II) Au(I), Cd(II), and Hg(II) have been synthesized in recent years in order to find simple model compounds for metalloproteins [82-90].

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Measurements

K_2PtCl_4 was purchased from Strem Chemicals, Inc. The deuterated solvents were purchased from Sigma-Aldrich Chemical Co. The thione ligands were prepared based on (Thorn et al., 1955 [91]) and (Maier et al., 1970 [92]) by the addition of the carbon disulfide to diamines in ether, the adduct was then refluxed at 100−110 °C for 2−3 hours and the clear yellow product was recrystallized from methanol. All other solvents were obtained from Fluka Chemical Co. and used without further purification. Elemental analysis for carbon, hydrogen, nitrogen and sulfur were performed on PerkinElmer 2400 Series II CHNS/O Elemental Analyzer. Infrared spectra were recorded in the range 4000–400 cm^{-1} as KBr discs using Nicolet 6700 FT-IR Spectrometer. The FT-Raman spectra of the platinum(II) complexes were obtained on NXR FT-Raman Module. The samples were studied in the solid state, placed in NMR tubes. A power of 500 mW was used and the spectra were recorded at 4 cm^{-1} resolution. ^{1}H NMR spectra were obtained on Jeol JNM-LA 500 NMR spectrometer operating at a frequency of 500.00 MHz. ^{13}C NMR spectra were obtained at the frequency of 125.65 MHz with ^{1}H broadband decoupling at 298 K. The spectral conditions were: 32k data points, 0.967 s acquisition time, 1.00 or 30.00 s pulse delay and 45^{o} pulse angle. Solid state cross-polarization magic-angle spinning (CPMAS) $^{195}Pt\{^{1}H\}$ NMR spectrum of complex **9B** was obtained

at ambient temperature on a Bruker 400 NMR spectrometer operating at a frequency of 85.94 MHz. Contact time of 3 ms was used with a proton pulse width of 4 μs, with a recycle delay of 10 s. Approximately 5000 FID's were collected and transformed with a line broadening of 100 Hz. Chemical shifts were referenced using an external sample of solid $K_2[PtCl_6]$. The sample was spun at 11 and 8 kHz at the magic angle to identify the center peak. The CPMAS spectra containing spinning side-band manifolds were analyzed using a computer software WSOLIDS developed at Dalhousie and Turbingen universities, to yield the anisotropy and asymmetry parameters [93]. The spectrum obtained at 11 kHz is shown in (Figure 6) and the NMR parameters are as follows: isotropic chemical shift = -3500 ppm; anisotropy = 2196 ppm and asymmetry = 0.71.

3.2 Preparation of complexes

3.2.1 Synthesis of PtL_2Cl_2 complexes

To a 10 cm^3 aqueous solution of K_2PtCl_4 (0.415 g, 1.00 mmol) was added dropwise a 15 cm^3 of an aqueous solution of thione ligand (2.00 mmol), immediately, a precipitate formed which after stirring at room temperature for 15 minutes was filtered, washed with cold water, ethanol and ether, then dried under vacuum at 30 ºC overnight. Thiones Et_2Imt (**6**), *i*-Pr_2Imt (**7**), EtMeImt (**8**) and EtDiaz (**10**) are slightly soluble in water, so they have been dissolved in a mixture of water and ethanol, and the reaction carried out in the same protocol. Analytical data are summarized in Table 1.

3.2.2 Synthesis of $[PtL_4]Cl_2$ complexes

For a hot aqueous solution (25 cm^3) of a thione ligand (2.00 mmol) was added a solution of K_2PtCl_4 (0.208 g, 0.500 mmol) in 3 cm^3 of water, the mixture was refluxed for 4 hours, during which time a clear yellow solution formed in most complexes. This was filtered whilst hot. Yellow crystals of **1B**, and **9B** suitable for X-ray diffraction analyses were obtained by slow evaporation of the solvent. Analytical data are summarized in Table 1.

Table 1. Elemental Analytical Data For The Platinum Complexes

Complex		Found (Calcd.) %				M.p. (°C)	Color	Yield %
		C	H	N	S			
1A	$[Pt(MeImt)_2Cl_2]$	19.10 (19.29)	3.31 (3.24)	11.14 (11.25)	12.52 (12.87)	180-182	Beige	91.2
1B	$[Pt(MeImt)_4]Cl_2.2H_2O$	24.91 (25.06)	4.61 (4.73)	14.51 (14.62)	16.36 (16.73)	262[a]	Yellow	58.9
2A	$[Pt(EtImt)_2Cl_2]$	22.89 (22.82)	3.88 (3.83)	10.51 (10.64)	12.07 (12.18)	154-155	Beige	98.9
2B	$[Pt(EtImt)_4]Cl_2$	30.56 (30.53)	5.01 (5.12)	14.46 (14.24)	16.47 (16.30)	225[a]	Yellow	64.3
3A	$[Pt(PrImt)_2Cl_2]$	25.71 (25.99)	4.12 (4.36)	9.98 (10.11)	11.25 (11.57)	150-107	Yellow	77.5
3B	$[Pt(PrImt)_4]Cl_2$	33.98 (34.20)	5.40 (5.47)	13.35 (13.30)	12.34 (12.22)	106[a]	Yellow	89.3
4A	$[Pt(i\text{-}PrImt)_2Cl_2]$	26.00 (25.99)	4.40 (4.36)	10.28 (10.11)	11.38 (11.57)	167-168	Brown	76.3
4B	$[Pt(i\text{-}PrImt)_4]Cl_2$	34.22 (34.20)	5.33 (5.47)	13.21 (13.30)	12.27 (12.22)	145-146	Yellow	92.5
5A	$[Pt(Me_2Imt)_2Cl_2]$	22.72 (22.82)	3.74 (3.83)	10.83 (10.64)	12.10 (12.18)	185-186	Yellow	78.1
6A	$[Pt(Et_2Imt)_2Cl_2]$	29.06 (28.87)	4.42 (4.33)	9.49 (9.62)	10.90 (11.01)	208-210	Yellow	24.0

7A	$[Pt(i\text{-}Pr_2Imt)_2Cl_2]$	33.61 (33.85)	5.54 (5.68)	8.64 (8.81)	10.30 (10.04)	183-185	Brown	40.5
8A	$[Pt(EtMeImt)_2Cl_2]$	25.82 (25.99)	4.26 (4.36)	10.23 (10.11)	11.72 (11.57)	150-151	Orange	42.0
9A	$[Pt(Diaz)_2Cl_2]$	19.17 (19.29)	3.39 (3.24)	11.36 (11.25)	13.00 (12.87)	213-215	Yellow	68.3
9B	$[Pt(Diaz)_4]Cl_2.H_2O$	26.00 (25.66)	4.39 (4.58)	15.10 (14.97)	17.44 (17.13)	250-252	Yellow	97.3
10A	$[Pt(EtDiaz)_2Cl_2]$	25.85 (25.99)	4.45 (4.36)	10.26 (10.11)	11.42 (11.57)	60-62	Orange	63.1
10B	$[Pt(EtDiaz)_4]Cl_2$	33.80 (34.19)	5.82 (5.74)	13.10 (13.29)	12.24 (12.22)	113-114	Yellow	52.5
11A	$[Pt(Diap)_2Cl_2]$	22.71 (22.82)	3.90 (3.83)	10.70 (10.64)	12.31 (12.18)	200-202	Yellow	97.0
11B	$[Pt(Diap)_4]Cl_2$	30.27 (30.53)	5.22 (5.12)	14.13 (14.24)	16.12 (16.30)	285 [a]	Yellow	35.3

[a] Decomposition point.

3.3 X-ray Crystallography

X-ray diffraction data were recorded on a Bruker-Axs Smart Apex system equipped with a graphite monochromatized Mo Kα radiation (λ = 0.71073 Å). The data were collected using SMART [94]. The data integration was performed using SAINT [95]. An empirical absorption correction was carried out using SADABS [96]. The structure was solved with the direct methods and refined by a full matrix least square methods based on F^2, using the structure determination package SHELXTL [97] based on SHELX 97 [98]. Graphics were generated using ORTEP-3 [99]. With the help of riding model Hydrogen atoms other than those of the water molecules, were included at calculated positions. Nitrogen atoms belonging to the NH groups were assumed to have a sp^2 hybridization.

For complex **1B**, the hydrogen atoms of the water molecules could not be located. For complex **9B,** one ligand carbon atom (C3) presents a two-site (C3A, C3B) disorder, the main component was refined to a site occupancy of 0.66(2). Hydrogen atoms of the water molecule were located on a Fourier Difference map and refined isotropically. Table 2 depicts the crystallographic data, while Table 7 shows the selected bond lengths and angles.

Table 2. Crystal And Structure Refinement Data For Compounds 1B & 9B

	1B	**2B**
CCDC deposit no.	902467	857990
Empirical formula	$C_{16}\ H_{36}\ Cl_2\ N_8\ O_2\ Pt\ S_4$	$C_{16}\ H_{34}\ Cl_2\ N_8\ O\ Pt\ S_4$
Formula weight	766.76	748.74
Temperature (K)	296(2)	301(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Monoclinic
Space group	P-1	$P2_1/c$
Unit cell dimensions		
a (Å)	9.011(2)	8.5945(4)
b (Å)	9.424(2)	14.2550(7)
c (Å)	9.627(2)	23.345(1)
α (°)	92.275(4)	90
β (°)	99.333(4)	91.383(1)
γ (°)	116.185(3)	90
Volume ($Å^3$)	718.2(3)	2859.2(2)
Z	1	4
Calc. density ($g.cm^{-3}$)	1.773	1.739
Absorp. coefficient (mm^{-1})	5.39	5.411
F(000)	380	1480
Crystal size (mm)	0.27 x 0.22 x 0.15	0.58 x 0.17 x 0.15
θ range (^{o})	2.16 - 28.37	1.67 - 28.29
Limiting indices	$-12 \le h \le 11$	$-11 \le h \le 11$
	$-12 \le k \le 12$	$-19 \le k \le 19$
	$-12 \le l \le 12$	$-31 \le l \le 31$
Max and min transmission	T_{min}= 0.3239, T_{max}= 0.4986	T_{min}= 0.1454, T_{max}= 0.4974
Data/restraints/parameters	3552 / 0 / 153	7104 / 44 / 308
Goodness-of-fit on F^2	1.041	1.040
Final R indices [I >2s(I)]	R_1 = 0.0255, wR_2 = 0.0543	R_1 = 0.0236, wR_2 = 0.0538
R indices (all data)	R_1 = 0.0259, wR_2 = 0.0545	R_1 = 0.0327, wR_2 = 0.0570
Largest diff. Peak and hole (e $Å^{-3}$)	1.310 and -0.842	1.048 and -0.406

CHAPTER 4

RESULTS AND DISCUSSION

4.1 Synthesis of the complexes

Based on the available analytical data, two types of complexes were synthesized. These are molecular compounds with a general formula $[PtL_2Cl_2]$, and ionic species with a formula of $[PtL_4]Cl_2$. The direct addition of a solution of potassium tetrachloroplatinate(II) K_2PtCl_4 (0.500 mmol) to hot aqueous solution of the thione ligand (**9)** (2.00 mmol) resulted in the formation of a yellow clear solution. After the mixture was refluxed for 4 hours, the solution was left at room temperature and yellow crystals suitable for X-ray structure determination were recovered after solvent evaporation. The other thiones immediately formed turbid mixtures when treated with K_2PtCl_4, which turned to clear solutions after reflux. A yellow crystalline product suitable for X-ray structure determination formed after solvent evaporation in case of ligand (**1**). When aqueous solutions of K_2PtCl_4 have been treated with thione ligands in a molar ratio of 1 : 2, immediately precipitates were formed. The resulted complexes are expected to have *trans* configuration based on the stereochemical regards and the stronger *trans* effect of the thione ligands [100, 101]. Unlike the free thione ligands which are soluble in most polar solvents, complexes **1A** and **2A** are only soluble in DMF, DMSO and slightly soluble in chloroform. The complexes formed are air-stable and therefore they could be kept for a long time in a desiccator without sign of decomposition.

4.2 Characterization of complexes

The most important IR frequencies are quoted in Table 3. As mentioned by many authors, the assignment of the thioamides absorptions of the free thiones and their related compounds is not straightforward [100, 102, 103]; this is due to the strong coupling between thiocarbonyl absorption with various bond absorptions in the fingerprint region in the IR spectrum [100, 102, 103]. Nevertheless, a strong and broad band in the range of 1400-1600 cm^{-1} appears for all the thione ligands and their related complexes. Based on available literature data, this band must be due to (N–H) deformation and (N–C–N) antisymmetric stretching. This band is often split and significantly shifted to higher frequency upon complexation; this is an indication of the increase in the double bond character of the C–N bond due to the coordination through sulfur [100, 103, 104]. The band observed in the range of the 3220–3300 cm^{-1} region for most of the thione ligands and their related complexes is directly assigned for N–H stretching vibrations [100, 102, 103, 105]. This band is shifted to higher frequencies for most of the platimun(II) complexes due to the increase in double bond character which also supports the idea of coordination through sulfur and indicates that in the solid state the thione form dominates. The assignment of thiocarbonyl frequencies is the most difficult part in the IR spectra because it strongly couples with other bonds within the molecule and gives rise to many bands in the fingerprint region. Many absorption bands in the IR spectrum of the free thiones, for instance **MeImt**: 1236, 1111, 957, 670, 637, 612, and 516 cm^{-1}, have shifted to lower wavenumber with no more than 21 cm^{-1} in its related compounds, and could be assigned to thiocarbonyl frequencies in various degrees [100]. The same

pattern of this shift has been noticed for most of the platinum complexes which indicate the presence of the platinum - sulfur bond.

The main Raman absorption bands of the complexes are summarized in Table 4, a strong and broad band in the range of 315−337 cm^{-1} is observed for all the complexes with general formula $[PtCl_2L_2]$ which has been assigned to Pt−Cl vibration [103, 106]. This band did not appear in the ionic compounds with the general formula $[PtL_4]Cl_2$. It may associate with a second vibration mode or in some complexes appears as shoulder that could be assigned to the presence of a *cis* configuration[103].

Finally, it seems appropriate to obtain more definitive evidence of the coordination site through another diagnostic tool, such as, NMR spectroscopy as well as X-ray crystallography, which will be discussed in the forthcoming parts.

Table 3. Selected IR absorption (cm^{-1}) the thiones and their Platinum(II) complexes

MeImt	3195mb	1527sh	1511s	1479s	1445sh	1296sb	1236m	1111m	957m	670m	637m	612m	516s		
1A	3282wb	1546s	1506s	1476m	1463m	1327s	1292s	1222w	1110m	955w	634w	591w	502w		
1B	3498w	3430w	3172wb	1541s	1512s	1470m	1324m	1293m	1109m	956w	636w	614w	567w	503w	
EtImt	3188wb	1510s	1480m	1465m	1450m	1321m	1256s	1132m	943w	790w	668w	616w	514w		
2A	3266mb	1531s	1506s	1475s	1317m	1278m	1254m	1122m	945w	787w	623w	500w			
2B	3447wb	3080wb		1533s	1509s	1471s	1316m	1281m	1249m	1119m	948w	791w	624w	499w	
PrImt	3206mb	1516sb	1479m	1460m	1308m	1241m	1195sh	1122	1035w	963w	674w	616s	515vs		
3A	3343wb	3201mb	1533s	1504s	1473m	1318m	1242m	1126w	1028w	959w	669w	616w	504w		
3B	3400wb	3202m	1533s	1502s	1475m	1437m	1315m	1281m	1244m	1026w	958w	662w	607mb	507w	
***i*-PrImt**	3209mb	1510s	1474s	1450s	1334m	1268s	1127w	1063s	964m	627sh	609s	526m			
4A	3267wb	1529s	1499s	1472s	1326m	1285s	1127w	1066s	958w	608m	521w				
4B	3313mb	1529s	1498s	1473s	1368m	1325m	1287m	1256sh	1128w	1065s	958m	607m	525w		

Me_2Imt	3445wb	1511mb	1484m	1446m	1396m	1325m	1286m	1220m	1134w	1113m	1067m	960w	641m	626m	507
5A	3447wb	1544s	1501m	1471w	1404w	1328s	1288m	1222w	1119m	954w	620m	491w			
Et_2Imt	3452wb	1504sb	1465s	1445s	1429s	1331m	1273sb	1195m	1124m	1067m	977w	783s	631sb	510s	
6A	3461wb	1573vs	1457m	1334mb	1291s	1210w	1105w	958w	790w	619w					
***i*-Pr_2Imt**	3453wb	1577w	1521m	1485m	1437m	1394m	1330s	1269s	1189m	1125s	1072s	1001m	640m	618w	590m
7A	3448wb	1636w	1518s	1486m	145m5	1366w	1324m	1281m	1172w	1128w	1076w	1026w	623w	602w	
EtMeImt	1506mb	1463mb	1393w	1334m	1270m	1205w	1120m	1085w	966w	779w	635s	620s	510vs		
8A	1580w	1542s	1503m	1461w	1330m	1279s	1202w	1128w	1099w	961w	797w	669w	633w	613w	494vw
Diaz	3210wb	1568sb	1479w	1430m	1361m	1317m	1206mb	1066m	970m	812m	769m	644m	567m	516m	
9A	3209wb	1573sh	1550s	1469w	1421m	1365s	1315s	1198s	1070w	973w	810m	739w	599m	523w	
9B	3238mb	1596s	1544s	1473s	1416m	1360s	1312s	1199s	1073w	973w	814m	753wb	617w	520w	
EtDiaz	3220mb	3024w	1539sb	1476w	1460w	1443m	1376m	1332m	1308m	1260m	1128m	1106m	705m	637m	509w
10A	3445wb	3155wb	1626s	1574s	1510sb	1437m	1374m	1315m	1257m	1129m	1105w	972w	690	564w	445w
10B	3408mb	3248mb	1580sb	1522m	1508m	1440m	1374m	1316m	1258m	1127m	1105w	971w	693w	565w	444w

Diap	3220wb	1564sb	1535sb	1453m	1355m	1324m	1213sb	922w	814m	757m	644m	526m			
11A	3338m	3208mb	1639w	1544sb	1438mb	1354m	1325m	1212vs	914w	809w	764	727	634m	521w	
11B	3202mb	1586m	1551sb	1456m	1439m	1351m	1324m	1222sb	919w	810m	760m	733w	669w	644m	520w

Abbreviations: w = weak, wb = weak & broad, m = medium, mb = medium & broad, s = strong, vs = very strong, sb = strong & broad, sh = shoulder

Table 4. Selected Raman absorption (cm^{-1}) frequencies for some of the platinum(II) complexes

Species	ν(M−Cl)
2A	327s
3A	316mb
4A	315sb
5A	322vs
6A	337sb 320sb
8A	333m 320sb
9A	327vs
10A	323mb
11A	324s

Abbreviations: m = medium, mb = medium & broad, s = strong, vs = very strong, sb = strong & broad.

The ^{1}H and ^{13}C NMR chemical shifts of the free thione ligands and their complexes were studied in $CDCl_3$. Complexes **1A** and **1B** are slightly soluble in chloroform, their ^{1}H and ^{13}C resonances were studied in DMSO. Complexes **2A**, **9B**, **11A** and **11B** have been dissolved in 50:50 (v/v) mixture of $CDCl_3$ and DMSO. The spectroscopic data are given in Table 5. In ^{1}H NMR spectrum, because these complexes are highly symmetrical arranged with respect to the coordination core; their coordinated ligands showed similar chemical shifts. The N–H protons of the coordinated thiones are shifted toward high frequency with respect to the free thiones. This large deshielding of the N–H protons is an indication of the increase in the double bond character of the C–N bond upon coordination to Pt(II) which is consistent with the coordination of thiourea or its derivatives to the metal [90, 103, 107]. The appearance of a N–H signal is an indication of coordinating to Pt(II) via the thione group. On the other hand, ^{13}C NMR signal for the thiocarbonyl carbon in the all complexes shifted upfield by 6.0 to 11.0 ppm with respect to the free ligands. This shift in thiocarbonyl carbon and NH proton signals is attributed

to the reduction in C=S bond order and increase in C–N bond order upon complexation [90, 103].

For solid state ^{13}C NMR spectra, Table 6, the complexation of Pt(II) with the thiones resulted in shielding of thiocarbonyl carbons in the obtained complexes by about 8 to 10 ppm in comparison with their free thione ligands [108]. This also confirms that the thione form is retained in the complexes. The diap ligand and the corresponding complexes showed 3 peaks in the thiocarbonyl region. This may be attributed to the different conformations of the 7-membered ring.

According to the solid state ^{15}N spectra, Table 6, the nitrogens in the synthesized compounds are about 5 to 8 ppm deshielded in comparison with their free ligands. ^{15}N NMR of the complexes **9B** and **11B** showed three and four different environments, respectively, which is corroborated by the X-ray structure, where the nitrogen atoms are in slightly different environments. Hence, it can be inferred that most of the complexes studied depict two crystallographically inequivalent complex molecules per unit cell or two nonequivalent ligands per complex molecule.

The potassium tetrachloroplatinate is reported to have an axial symmetry, and the tensor has a very large chemical shift anisotropy of 10414 ppm [109]. The ^{195}Pt NMR of complex **9B** lies in the same range observed for other Pt(II) complexes surrounded by four sulfur containing ligands in square planar geometry [110, 111]. The observed low anisotropy in our complex may be attributed to the deviation from the perfect axial symmetry. We were unable to record platinum spectra for the other complexes, presumably due to their large chemical shift anisotropies.

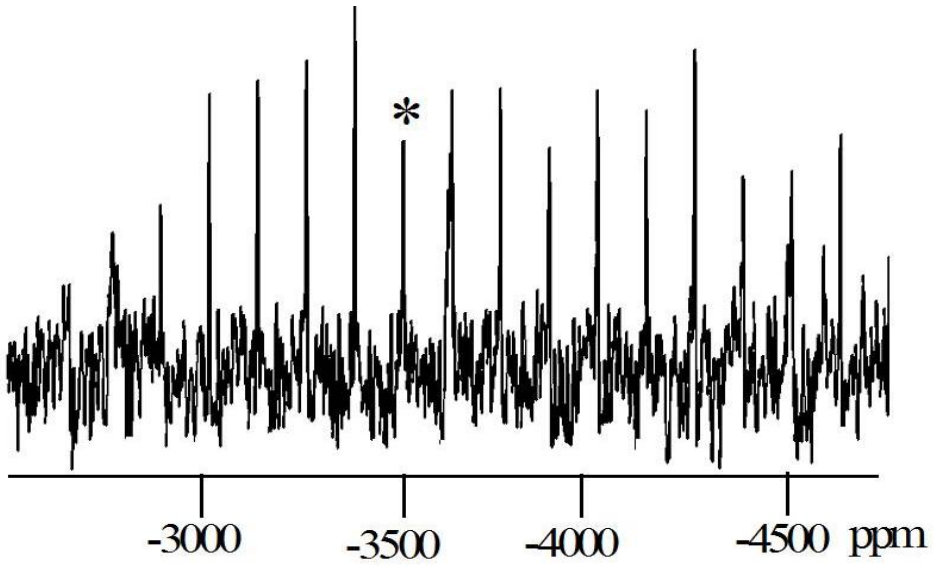


Figure 6. ^{195}Pt CPMAS spectrum of 9B at a spinning rate of 11kHz. The isotropic peak is marked *

Table 5. ^{1}H and ^{13}C chemical shifts (ppm) of the thiones and their Pt(II)-thione complexes in $CDCl_3$

Species	N–H	C–2	C–4	C–5	C–6	N–C1	N–C2
MeImt[a]	8.02	182.90	40.60	50.18		33.39	
1A[a]	9.41 8.76[f]	173.67	42.44	51.93		33.51	
1B[a]	9.41	173.55	42.27	51.68		33.60	
EtImt[b]	5.67	183.02	41.56	47.85		41.23	12.02
2A[c]	9.40	173.48	42.48	48.80		41.40	12.15
2B	9.67	174.41	42.78	49.11		41.78	12.44
PrImt[b]	5.88	183.72	41.38	48.63		48.63	20.44 11.18[d]
3A	9.71	175.18	42.74	50.06		48.59	20.70 11.19[d]
3B	9.58	174.90	42.80	49.66		48.48	20.60 11.09[d]
***i*-PrImt**[b]	5.63	182.51	41.48	42.85		46.90	19.32
4A	10.02 9.64[f]	174.23	42.61	43.72		47.26	19.73
4B	9.65	173.89	42.73	44.00		47.59	19.68
Me_2Imt	-	183.56	48.31	48.31		35.14	
5A	-	177.70	48.96	48.96		35.95	
Et_2Imt	-	181.88	42.19	42.19		45.31	12.01

6A[c]	-	171.53	43.22	43.22		46.29	12.38
***i*-Pr$_2$Imt**	-	180.88	40.46	40.46		46.88	19.16
7A	-	174.43	40.94	40.94		48.10	19.74
EtMeImt	-	182.47	42.30	45.16		48.21 34.71[e]	11.19
8A	-	176.97	43.38	45.97		48.94 35.79[e]	12.55
Diaz[b]	6.75	176.81	40.59	19.30	40.59		
9A[c]	9.13	167.86	40.39	18.93	40.39		
9B[c]	9.08	167.68	40.15	18.86	40.15		
EtDiaz[b]	6.31	176.88	45.41	21.00	40.73	48.92	11.99
10A	9.62	168.91	46.43	20.41	40.72	48.89	12.77
10B	9.39	168.55	46.90	20.56	40.38	49.08	12.76
Diap[b]	6.69	189.42	46.28	27.33	27.33		
11A[c]	9.09	178.03	46.25	26.42	26.42		
11B[c]	9.09	178.27	46.25	26.43	26.43		

[a] ^{1}H and ^{13}C resonances in DMSO.

[b] ^{1}H and ^{13}C resonances of these thiones in DMSO are reported in literature [107].

[c] ^{1}H and ^{13}C resonances of these complexes in 50:50 (v/v) mixture of $CDCl_3$ and DMSO.

[d] N–C3

[e] Resonance due to $CH_3^{/}$ group

[f] ^{1}H resonance due to nonequivalent amino groups protons

Table 6. ^{15}N and ^{13}C solid NMR chemical shifts (ppm) for the ligands and their Pt(II) complexes

Species	N–1	C–2	C–4	C–5	C–6	N–C1	N–C2
MeImt	-275.29 -277.41[a]	180.97	40.68	50.85			34.19
1A	-271.43	171.32	44.05	52.21			34.51
1B	-269.03 -279.95[a]	173.03	43.32	52.50			35.07 32.90[b]
Diaz	-273.43	175.22	39.79	19.90	39.79		
9A	-265.79	-	41.29	19.23	41.29		
9B	-265.15	168.38	42.39	20.96	42.39		
	-270.26[a]	167.38	41.60	19.91	41.6		
	-274.87[a]	166.41					
EtDiaz	-271.38 -274.85[a]	175.76	41.62	21.58	46.68	46.68	12.77
10B	-258.24 -270.75[a]	168.82	41.58	20.69	48.4	48.4	12.73
		166.60					
Diap	-265.55	188.22	48.62	27.80	27.80		
		186.17	45.75				
		183.08	44.50				
11A	-265.77	168.20	47.24	27.20	27.20		
11B	-259.12 -263.62[a]	181.70	48.47	28.38	28.38		
		180.16	45.81	23.97	23.97		
		174.79	43.35				

[a] Resonance due to nonequivalent amino groups

[b] Resonance due to nonequivalent CH_3 group

4.3 X-ray crystal structure

4.3.1 Crystal structure of compound 1B

The platinum (II) ion is located on an inversion center and bound to the S atoms of four N-methylimidazolidine-2-thione (**MeImt**) ligand molecules in a distorted square planar geometry. The Pt-S bond distances are 2.3243(9) Å and 2.3263(9) Å and the S-Pt-S bond angle is 92.11(3)°. These values are in agreement with those reported for the complex tetrakis(Imidazolidine-2-thione)-platinum(II) di-iodide [112]. The SCN_2 moieties of the two ligand molecules are essentially planar with the following bond lengths (d(S1-C1) = 1.705(4)Å, d(C1-N1) = 1.321(5) Å, d(C1-N2) = 1.468(5) Å) and (d(S2-C5) = 1.709(3)Å, d(C5-N3) = 1.313(5) Å, d(C5-N4) = 1.333(4) Å). The N-H groups (N1-H1 and N3-H3) are engaged in hydrogen bonding with the chloride ions. The ORTEP atomic labeling scheme is given in Figure 7.

4.3.2 Crystal structure of compound 9B

To the best of our knowledge, this is the first X-ray structure of a platinum complex based on 1,3-Diazinane-2-thione (**Diaz**) ligand [113]. In this compound, Pt(II) ion is bonded to four sulfur atoms, each belonging to a **Diaz** ligand in a distorted square planar geometry. The Pt-S bond lengths are in the range 2.3111(8)-2.3321(8) Å while the S-Pt-S bond angles are in the range 87.99(3)-93.67(3) °. These values are similar to those found for tetrakis(thiourea-S)-platinum(II) dichloride [114] and tetrakis(1-Methyl-4-imidazoline-2-thione)-platinum(II) dichloride dehydrate [115]. The SCN_2 moieties of the four ligand molecules are essentially planar with the S-C and C-N bond lengths in the ranges (1.722(3)-1.744(3) Å) and (1.304(4)-1.324(4) Å) respectively. The corresponding

bond lengths noted for the free ligand are (d(S-C) = 1.720 Å, d(C-N) = 1.331 Å) [116]. The significantly longer S-C bond distances, associated with shorter C-N bonds in the complex, are consistent with significant C-N double bond character and electron donation from the ligand to the metal ion. Each of the four **Diaz** ligands is engaged in hydrogen bonding interactions with one chloride counter ion (Cl1). This results in an umbrella type structure where all tetrahydropyrimidine rings are on the same side of the PtS4 mean plane (Figure 8). Other hydrogen bonding interactions also take place including those with a water molecule present in the lattice (Figure 9).

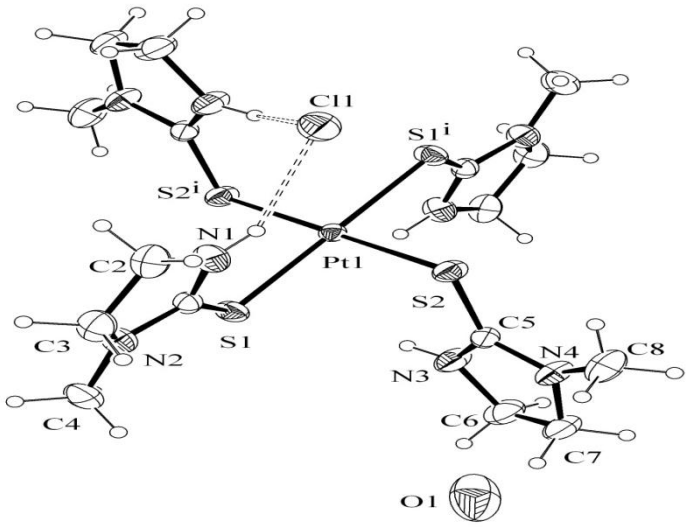


Figure 7. ORTEP diagram of 1B showing the atomic labeling scheme. Displacement ellipsoids are drawn at the 30% probability level

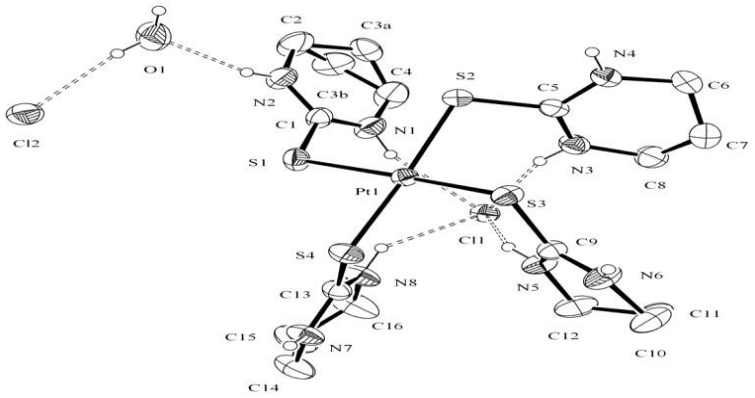


Figure 8. ORTEP diagram of 9B showing the atomic labeling scheme. Displacement ellipsoids are drawn at the 30% probability level. Methylene hydrogen atoms have been omitted for clarity

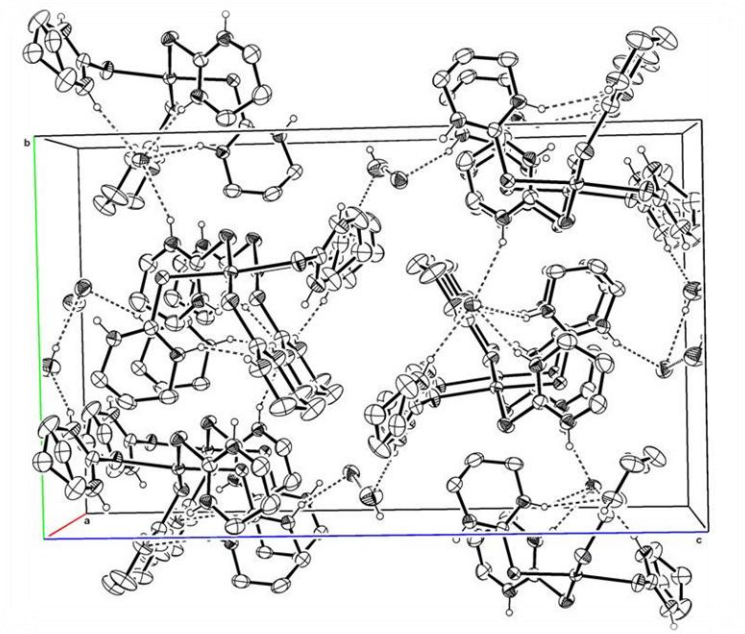


Figure 9. Molecular packing in 9B showing part of the hydrogen bonding pattern

Table 7. Selected bond lengths (Å) and bond angles (°) for compounds 1B & 9B

1B				**9B**			
Bond lengths		**Bond angles**		**Bond lengths**		**Bond angles**	
Pt1-S1	2.3243(9)	S1-Pt1-S2	92.11(3)	Pt1-S3	2.3111(8)	S3-Pt1-S1	171.53(3)
Pt1-S2	2.3263(9)	S1-Pt1-S2^{i}	87.89(3)	Pt1-S1	2.3240(8)	S3-Pt1-S4	87.99(3)
S1-C1	1.705(4)			Pt1-S4	2.3263(8)	S1-Pt1-S4	88.01(3)
S2-C5	1.709(3)	N1-C1-N2	110.2(3)	Pt1-S2	2.3321(8)	S3-Pt1-S2	89.25(3)
		N3-C5-N4	110.2(3)			S1-Pt1-S2	93.67(3)
N1-C1	1.321(5)					S4-Pt1-S2	171.72(3)
N2-C1	1.330(4)						
N3-C5	1.313(5)						
N4-C5	1.333(4)						

Symmetry code: i = 2-x, 2-y, -z

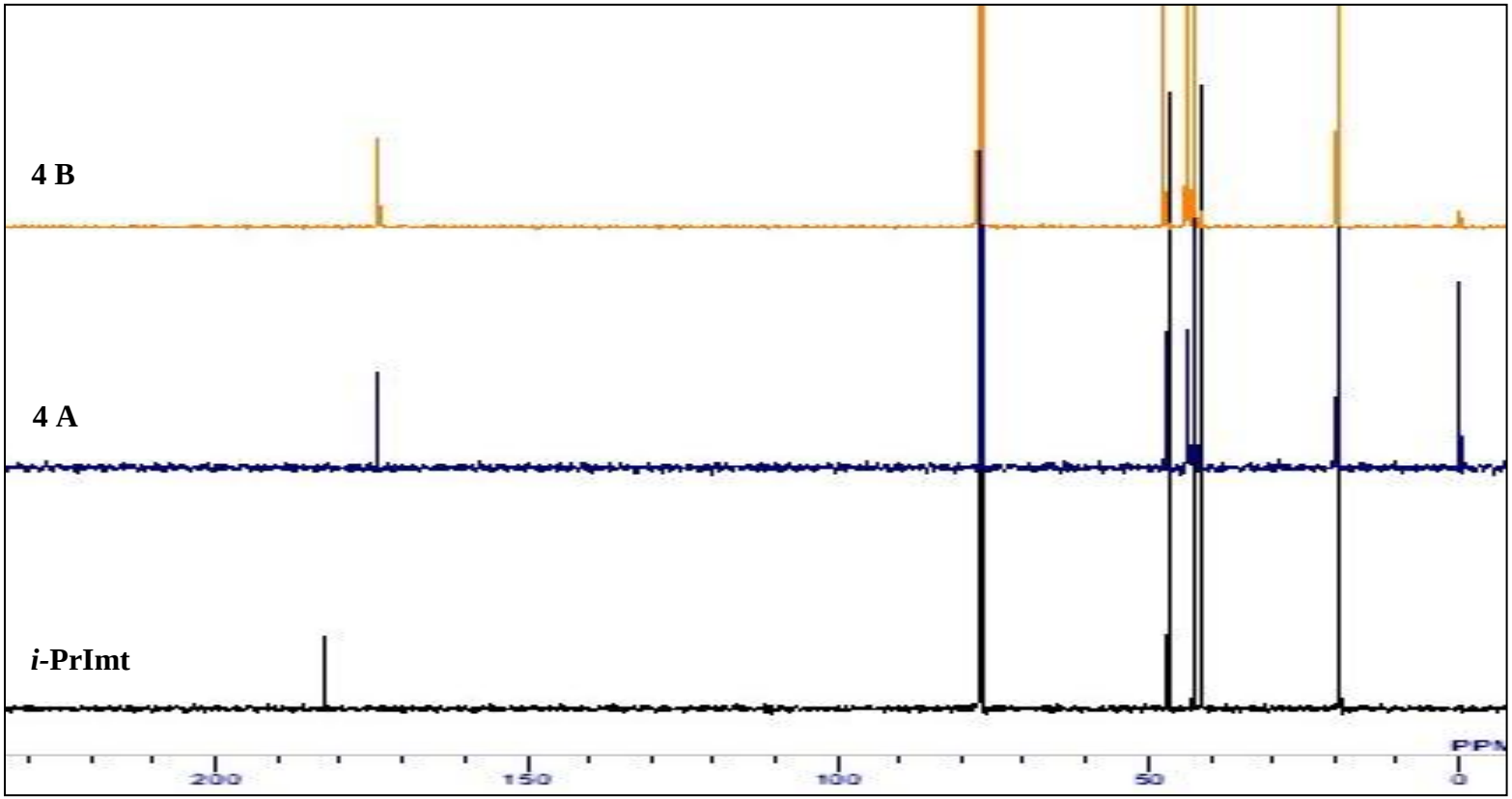
CHAPTER 5

CONCLUSION AND RECOMMENDATION

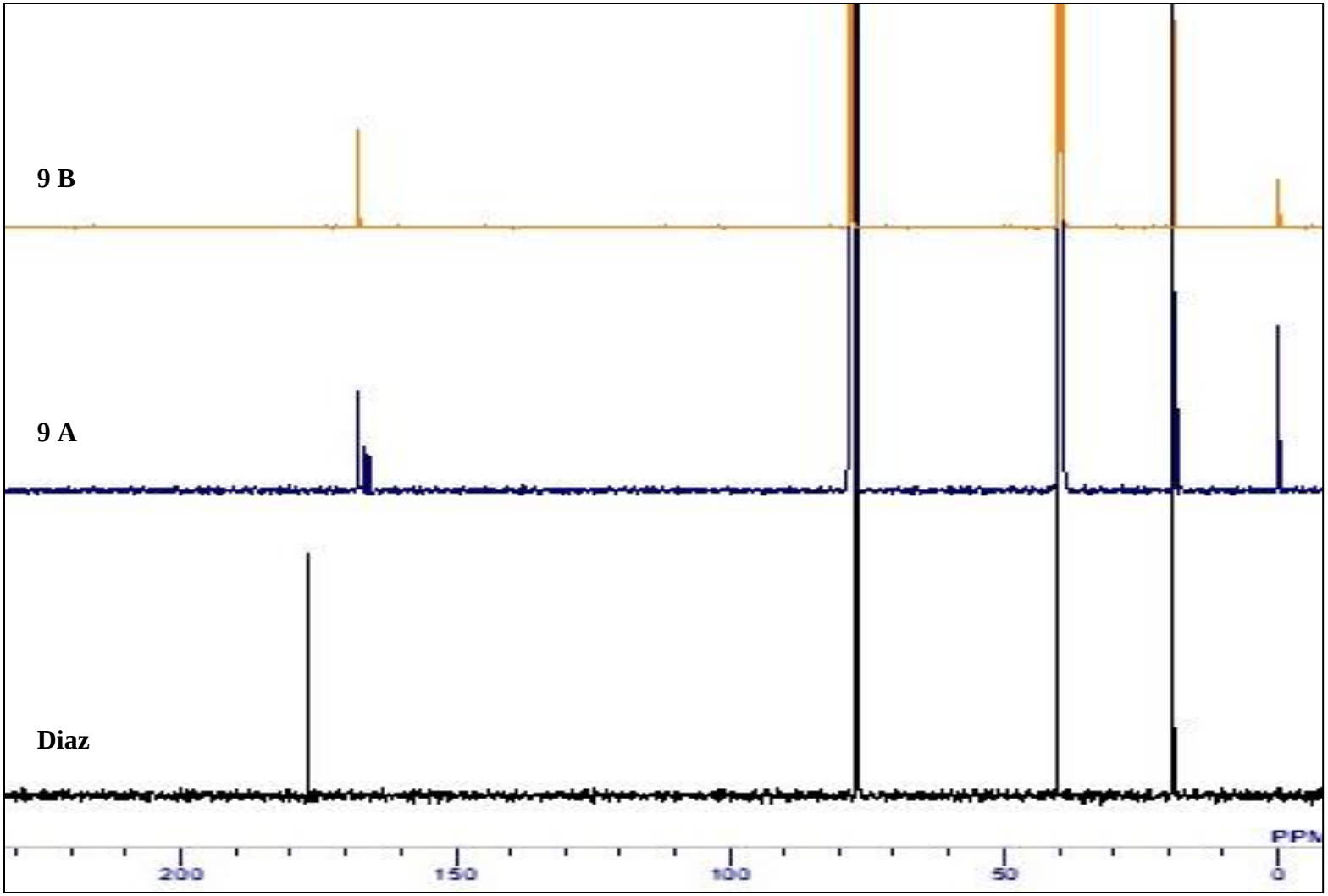
We successfully synthesized a series of molecular compounds with a general formula $[PtL_2Cl_2]$, and ionic species with a formula of $[PtL_4]Cl_2$, and fully characterized them using various analytical techniques. NMR as well as X-ray crystallography confirmed that the Pt(II) ion is bonded to the thione ligands through their sulfur atoms. It was discovered that hydrogen bonding is an important factor that affect the stability of these complexes. Steric effect was found to play an important role in the synthesis of these complexes; highly steric ligands prefer to form complexes in general formula $[PtL_2Cl_2]$, while the less steric ligands could form the two formulas.

For the application of the synthesized complexes, we recommend that more work be done to study their efficacy against cancer cell models as well as their putative biological targets.

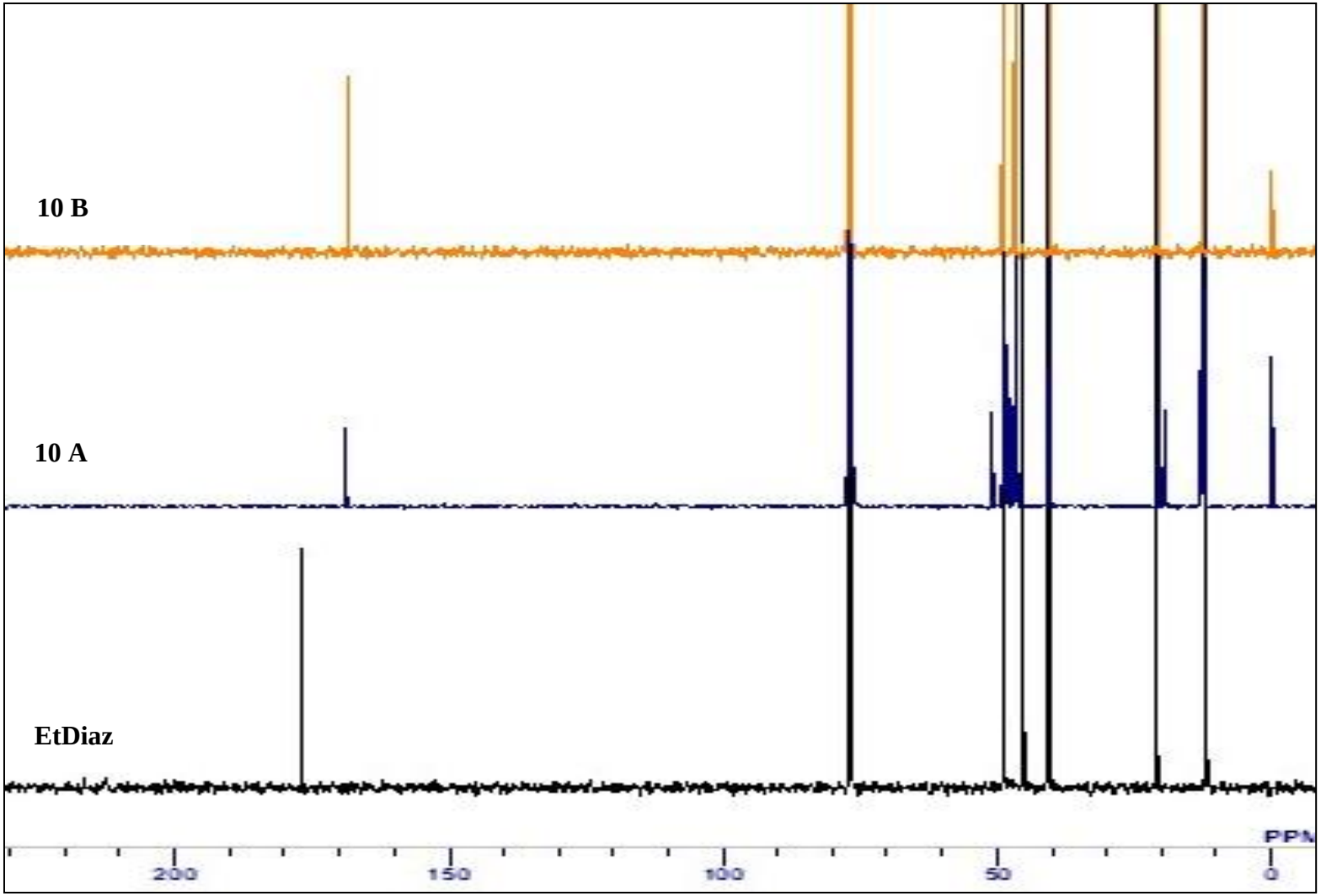
Appendix A
^{13}C solution NMR



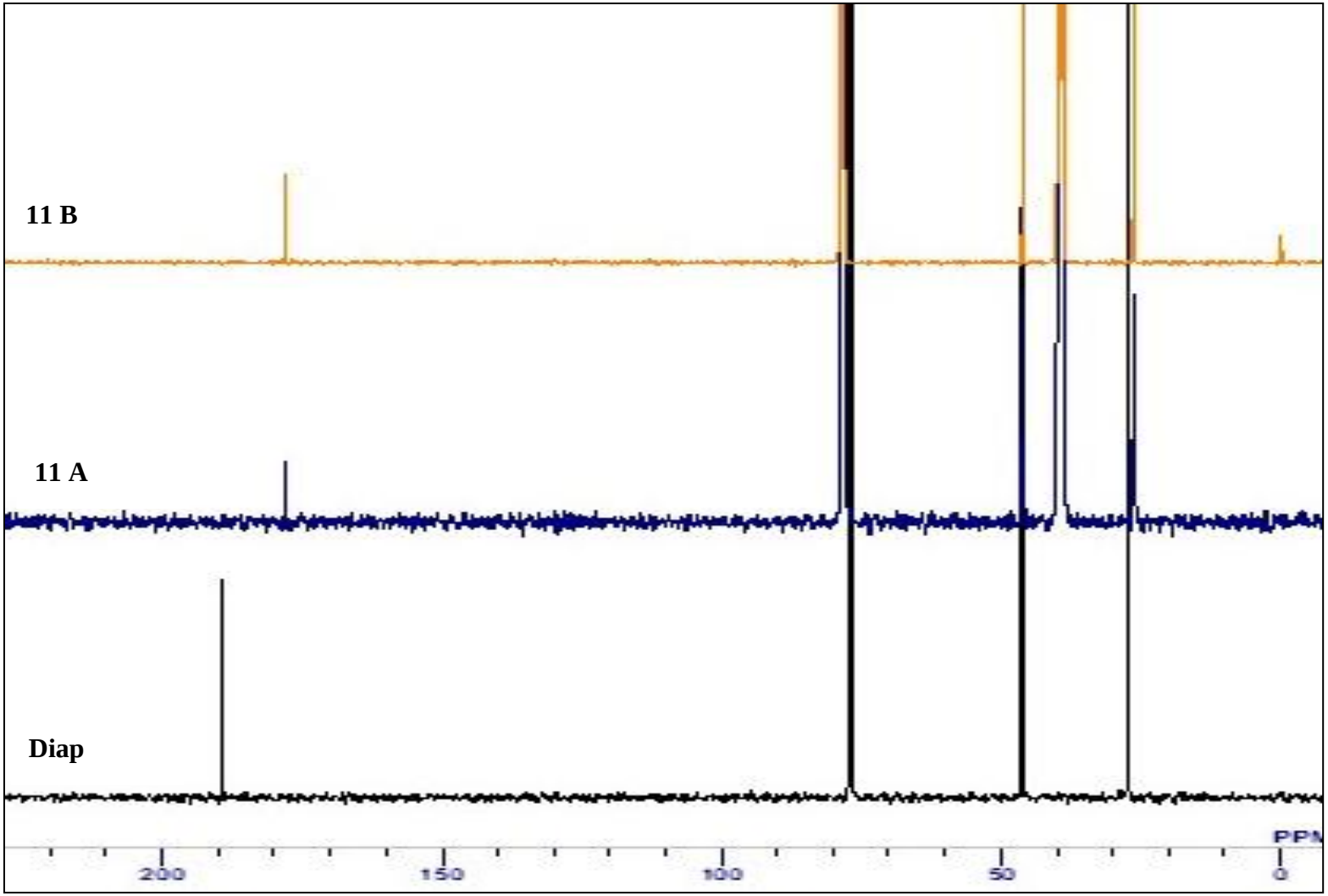
^{13}C chemical shifts (ppm) of *i*-PrImt and its Pt(II) complexes in $CDCl_3$



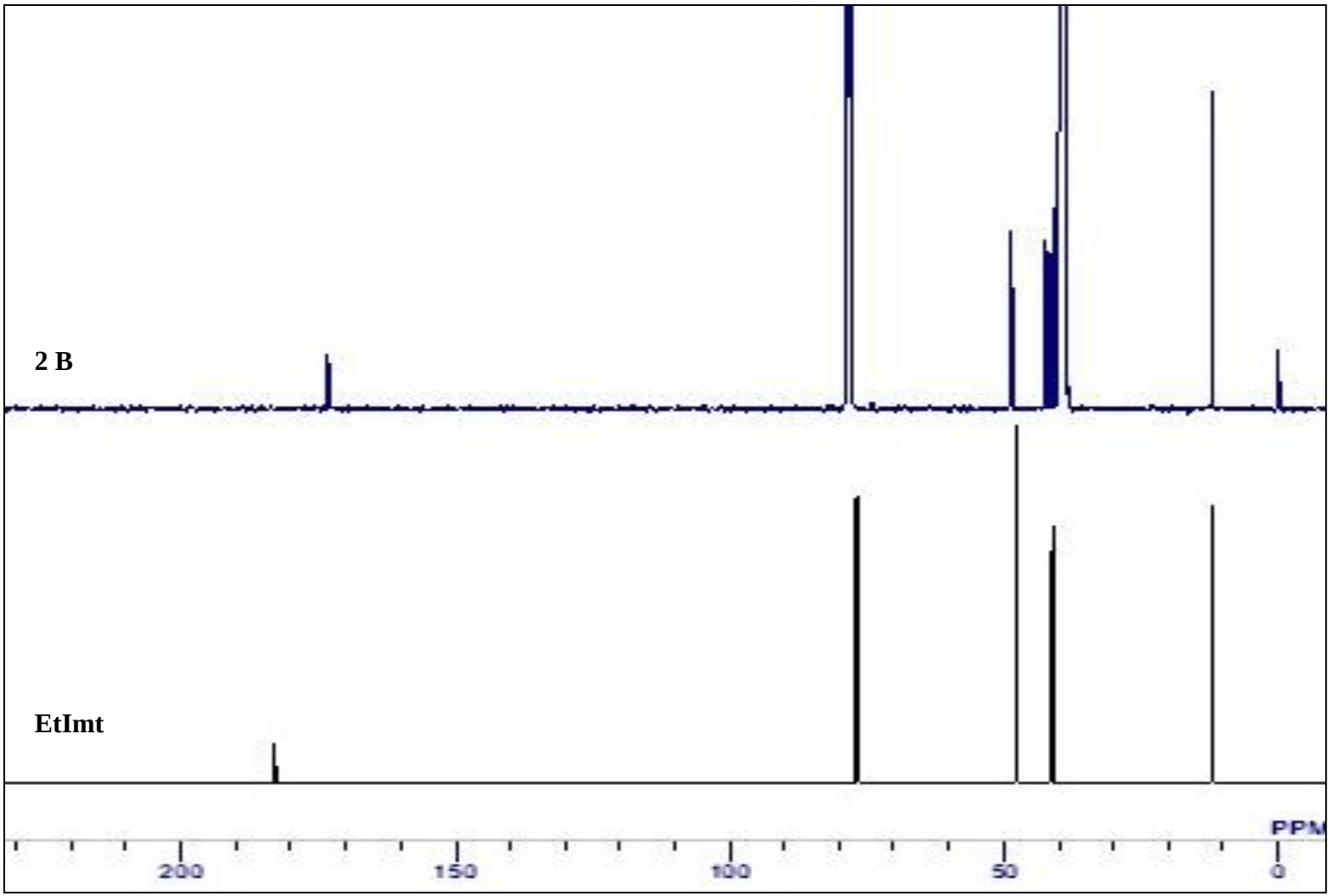
^{13}C chemical shifts (ppm) of Diaz and its Pt(II) complexes in a mixture of $CDCl_3$ & DMSO-d_6.



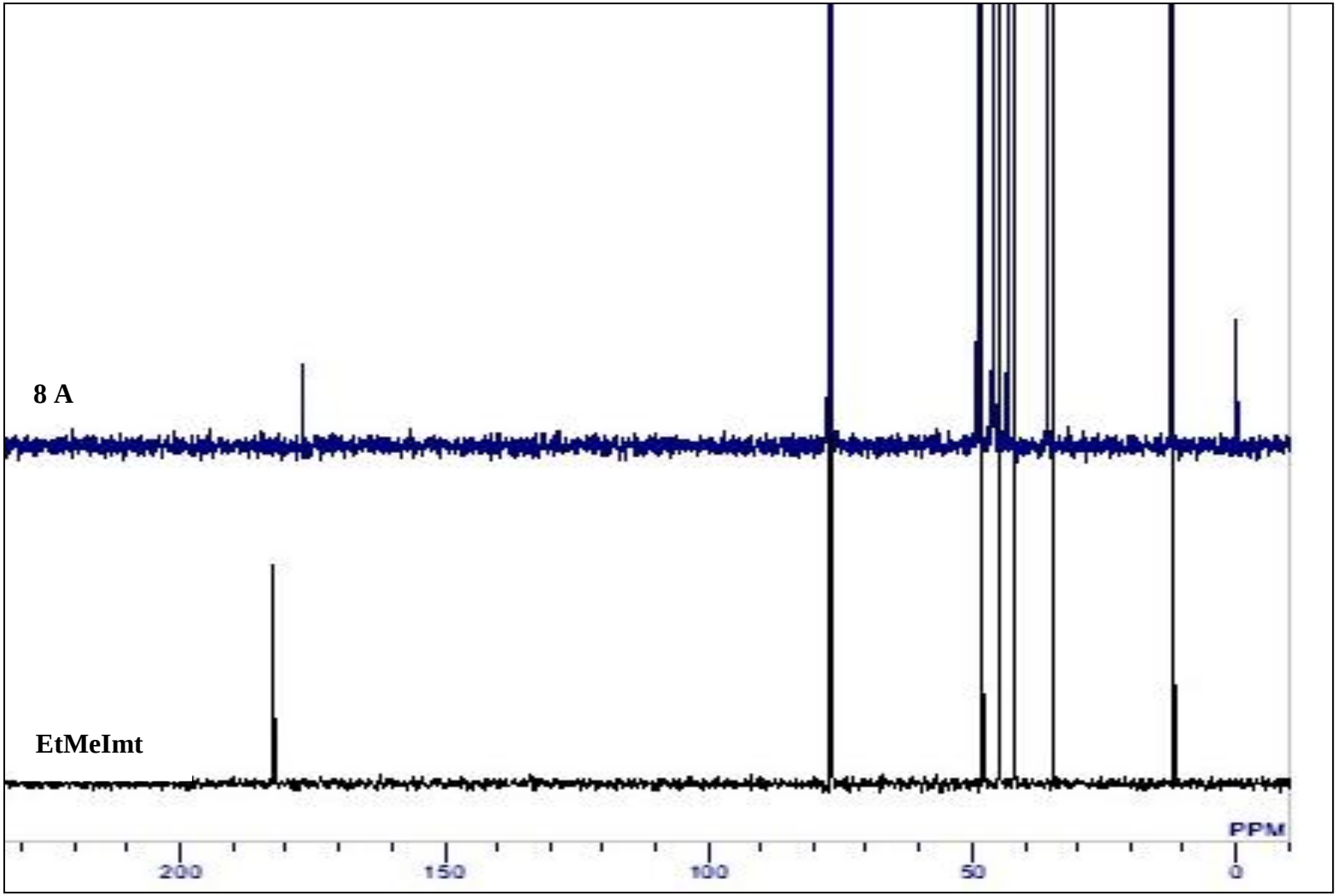
^{13}C chemical shifts (ppm) of EtDiaz and its Pt(II) complexes in $CDCl_3$.



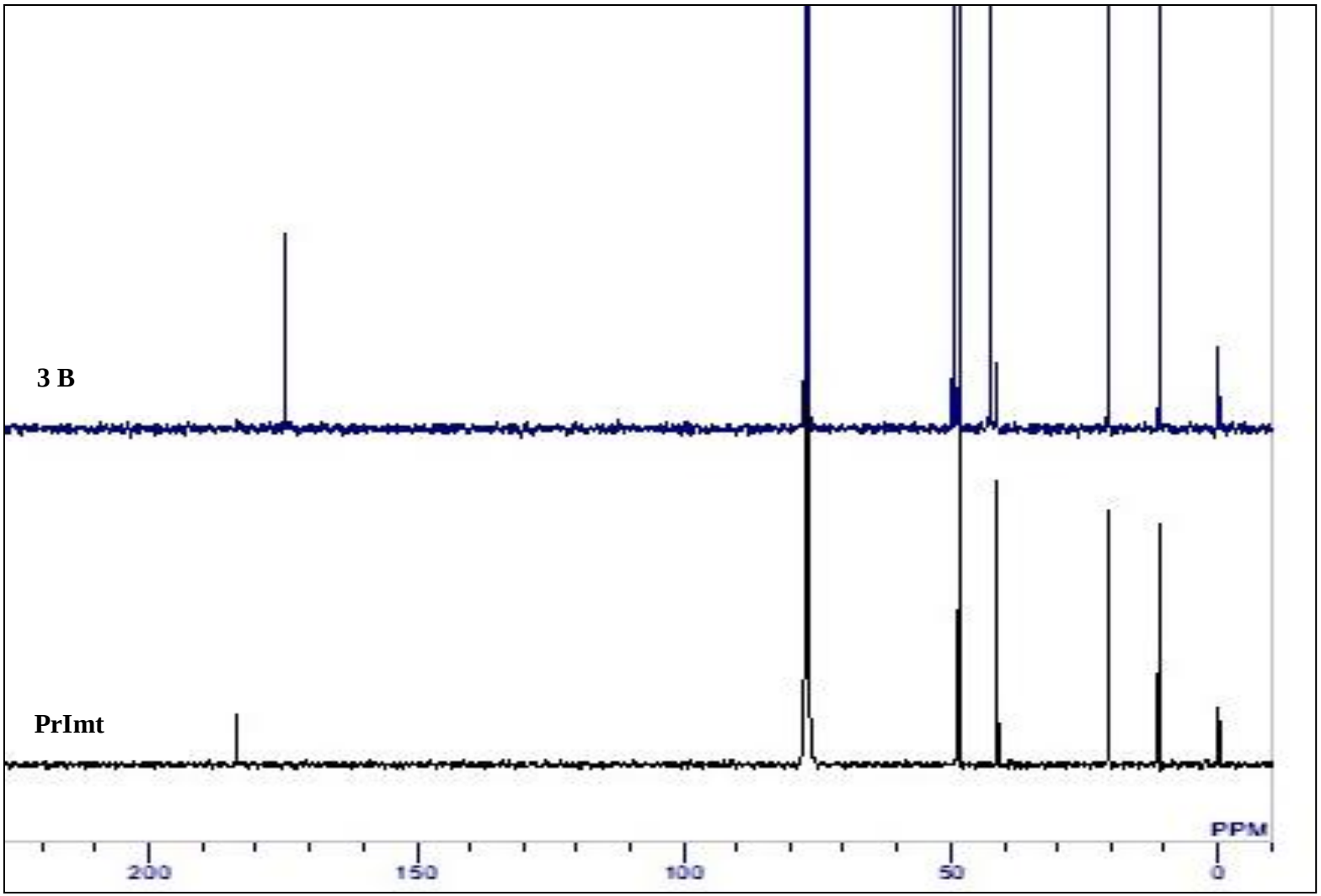
^{13}C chemical shifts (ppm) of Diap and its Pt(II) complexes in a mixture of $CDCl_3$ & DMSO-d_6.



^{13}C chemical shifts (ppm) of EtImt and its Pt(II) complexes in a mixture of $CDCl_3$ & DMSO-d_6.

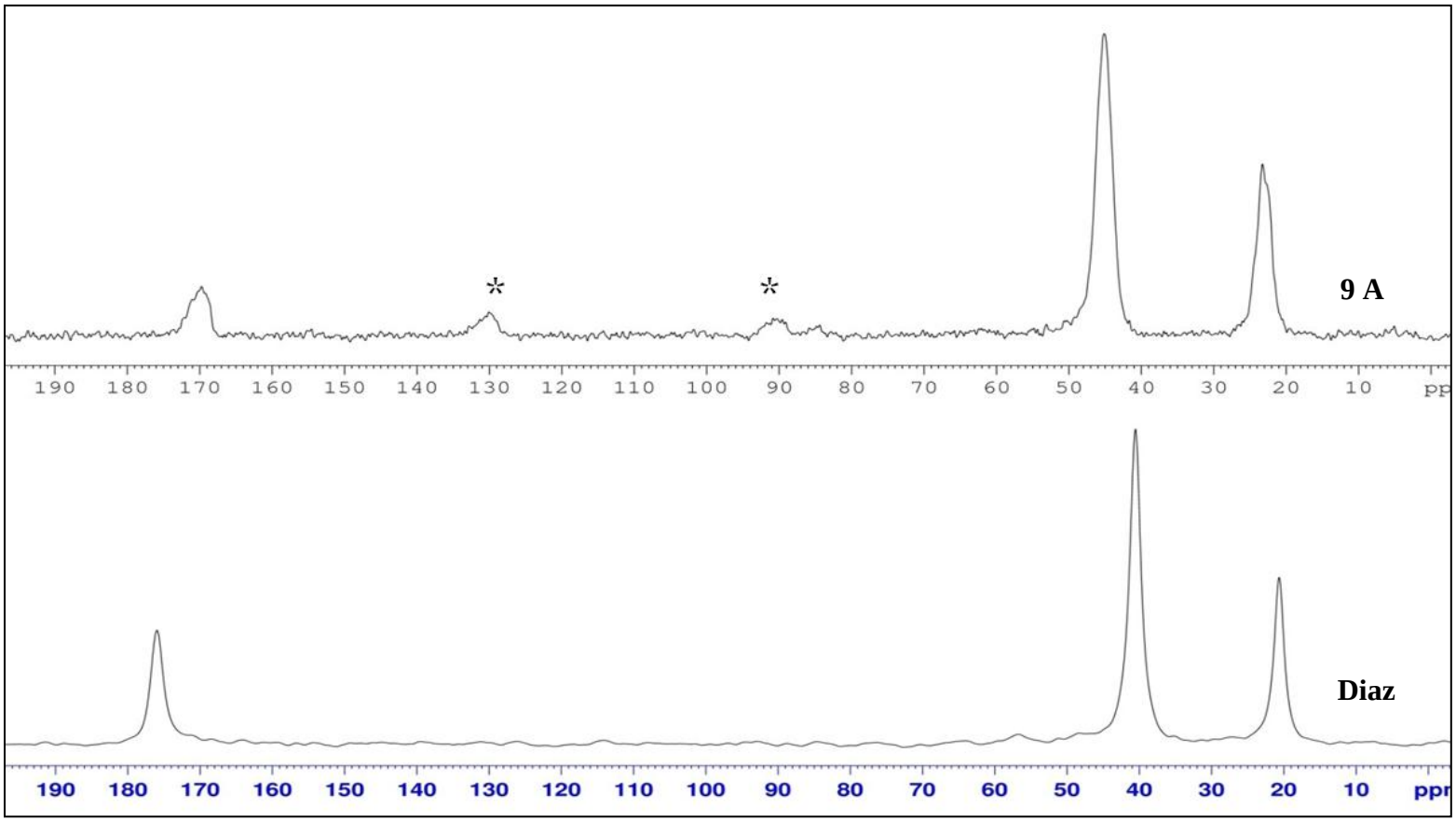


^{13}C chemical shifts (ppm) of EtMeImt and its Pt(II) complex in $CDCl_3$.

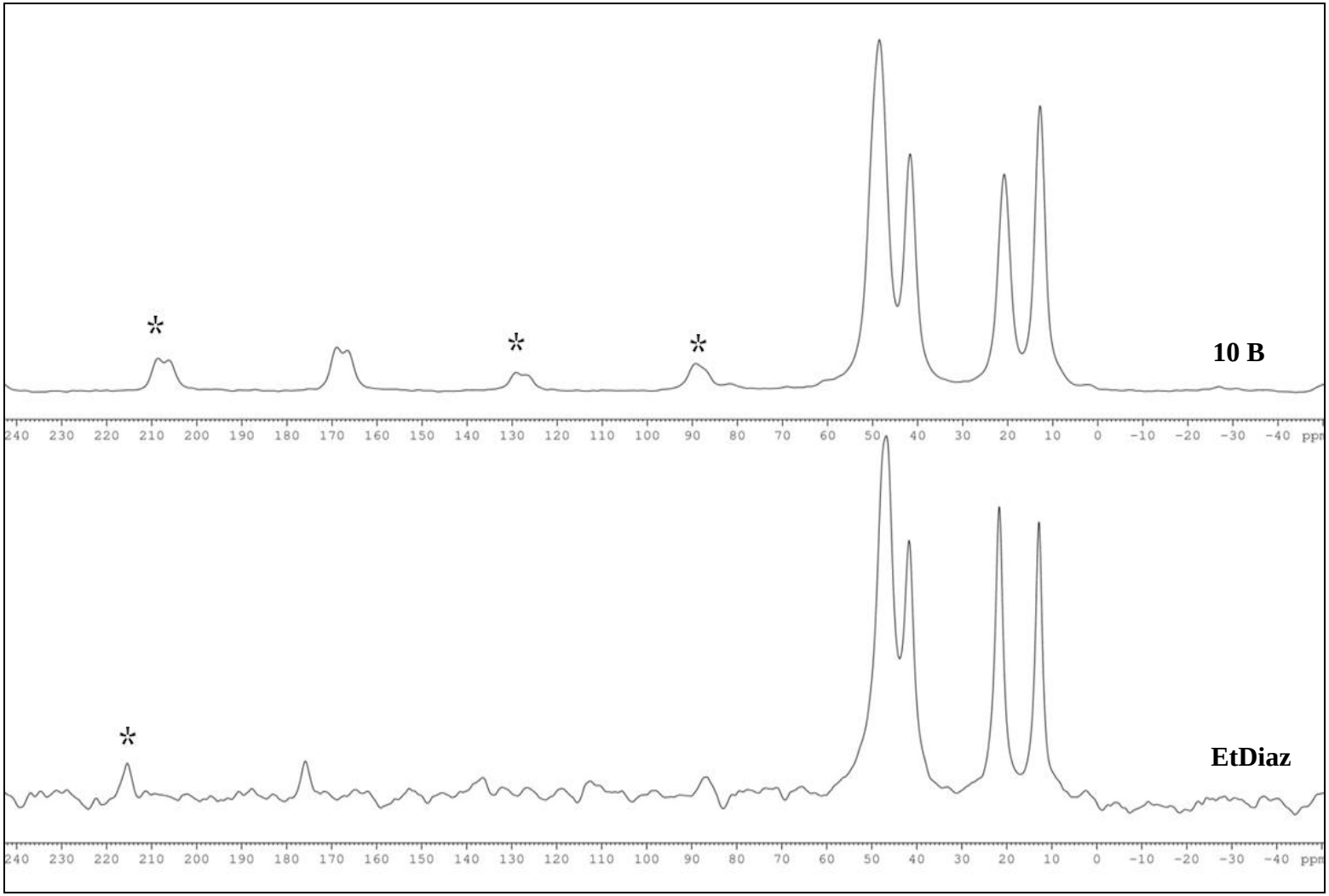


^{13}C chemical shifts (ppm) of PrImt and its Pt(II) complex in $CDCl_3$.

Appendix B
^{13}C solid state NMR

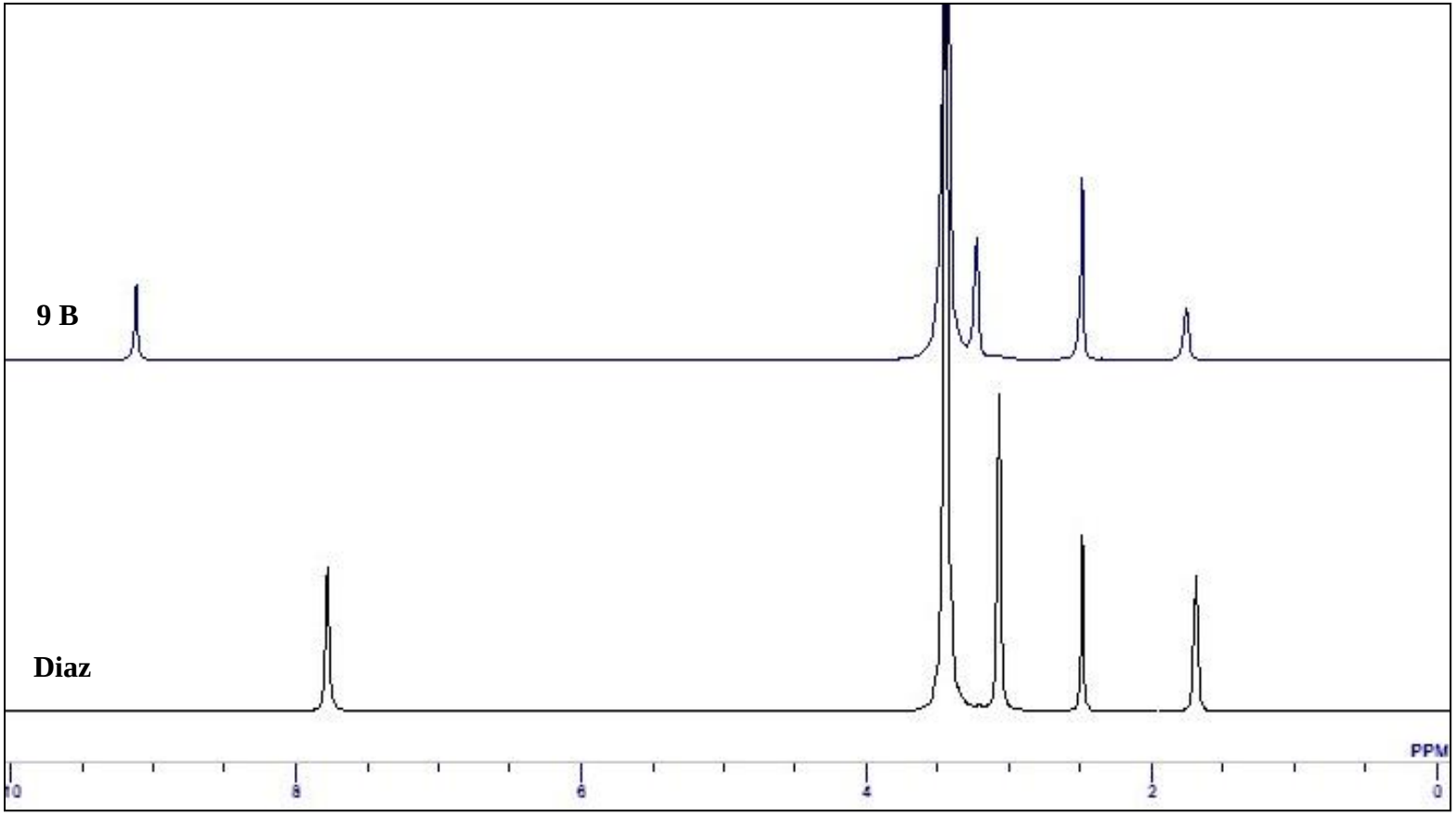


^{13}C solid NMR chemical shifts (ppm) of Diaz and its Pt(II) complex. The spinning sidebands are marked *.

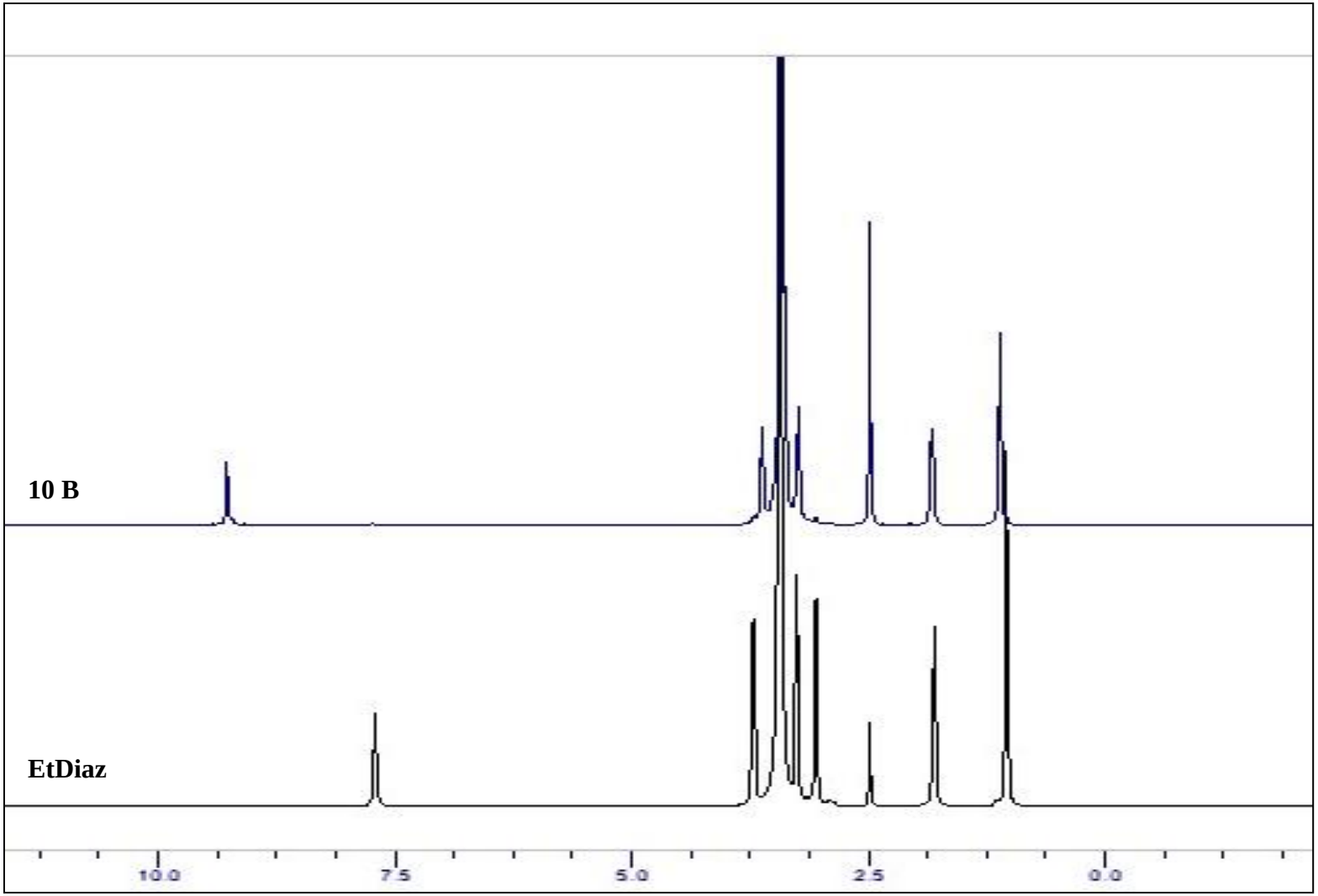


^{13}C solid NMR chemical shifts (ppm) of EtDiaz and its Pt(II) complex. The spinning sidebands are marked *.

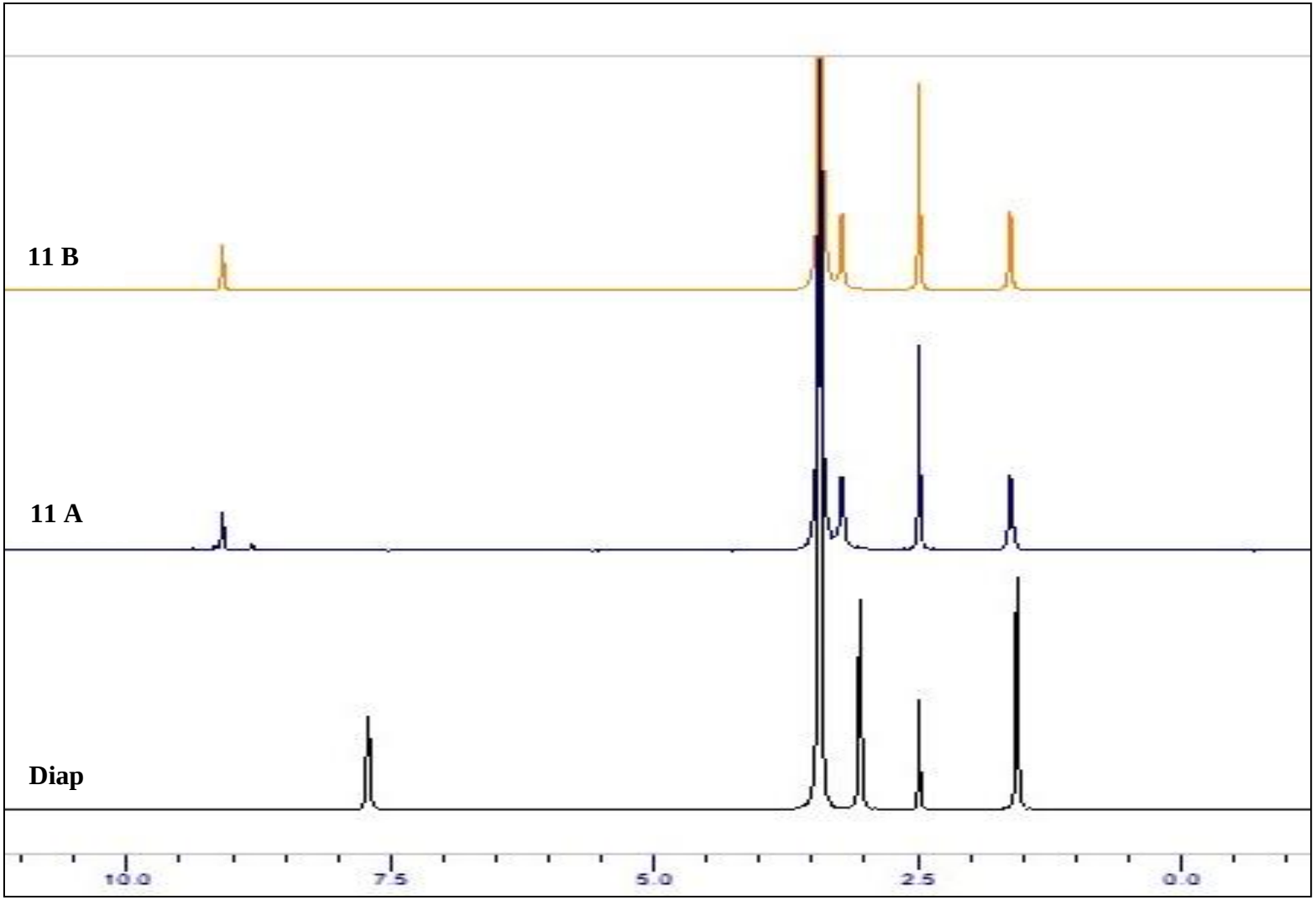
Appendix C
^{1}H solution NMR



^{1}H chemical shifts (ppm) of Diaz and its Pt(II) complexes in DMSO-d_6.



^{1}H chemical shifts (ppm) of EtDiaz and its Pt(II) complexes in DMSO-d_6.



^{1}H chemical shifts (ppm) of Diap and its Pt(II) complexes in DMSO-d_6.

References

[1] B. Rosenberg, L. VanCamp, and T. Krigas, Nature 205 (1965) 698.

[2] E. Wong and C. M. Giandomenico, Chemical Reviews 99 (1999) 2451.

[3] L. H. Einhorn and J. Donohue, Annals of Internal Medicine 87 (1977) 293.

[4] R. F. Ozols, Cancer Treatment Reviews 18, Supplement A (1991) 77.

[5] A. M. Pizarro and P. J. Sadler, Biochimie 91 (2009) 1198.

[6] M. Goren, R. Wright, and M. Horowitz, Cancer Chemotherapy and Pharmacology 18 (1986) 69.

[7] L. R. Kelland, G. Abel, M. J. McKeage, M. Jones, P. M. Goddard, M. Valenti, B. A. Murrer, and K. R. Harrap, Cancer Research 53 (1993) 2581.

[8] R. Weiss and M. Christian, Drugs 46 (1993) 360.

[9] D. Lebwohl and R. Canetta, European journal of cancer (Oxford, England : 1990) 34 (1998) 1522.

[10] J. Reedijk, Chemical Reviews 99 (1999) 2499.

[11] A. Muscella, N. Calabriso, S. A. De Pascali, L. Urso, A. Ciccarese, F. P. Fanizzi, D. Migoni, and S. Marsigliante, Biochemical Pharmacology 74 (2007) 28.

[12] W. Friebolin, G. Schilling, M. Zöller, and E. Amtmann, Journal of Medicinal Chemistry 47 (2004) 2256.

[13] A. A. Ali, H. Nimir, C. Aktas, V. Huch, U. Rauch, K.-H. Schäfer, and M. Veith, Organometallics 31 (2012) 2256.

[14] R. del Campo, J. J. Criado, E. García, M. a. R. Hermosa, A. Jiménez-Sánchez, J. L. Manzano, E. Monte, E. Rodríguez-Fernández, and F. Sanz, Journal of Inorganic Biochemistry 89 (2002) 74.

[15] J. Ren, J. Diprose, J. Warren, R. M. Esnouf, L. E. Bird, S. Ikemizu, M. Slater, J. Milton, J. Balzarini, D. I. Stuart, and D. K. Stammers, Journal of Biological Chemistry 275 (2000) 5633.

[16] Z. Ma, L. Rao, and U. Bierbach, Journal of Medicinal Chemistry 52 (2009) 3424.

[17] J. M. Brow, C. R. Pleatman, and U. Bierbach, Bioorganic & Medicinal Chemistry Letters 12 (2002) 2953.

[18] X. Yao, K. Panichpisal, N. Kurtzman, and K. Nugent, The American journal of the medical sciences 334 (2007) 115.

[19] R. Girling, K. Chatterjee, and E. Amma, Inorganica Chimica Acta 7 (1973) 557.

[20] M. E. O'Neill, E. S. Raper, J. A. Daniels, and I. W. Nowell, Inorganica Chimica Acta 66 (1982) 79.

[21] J. Calvo, J. S. Casas, E. García-Martínez, Y. Parajó, A. Sánchez-González, and J. Sordo, Zeitschrift für anorganische und allgemeine Chemie 630 (2004) 215.

[22] C. J. Jones and J. Thornback, Medicinal Applications of Coordination Chemistry, Royal Society of Chemistry, 2007.

[23] S. Gibaud and G. Jaouen, in Medicinal Organometallic Chemistry, Vol. 32 (G. Jaouen and N. Metzler-Nolte, eds.), Springer Berlin Heidelberg, 2010, p. 1.

[24] R. D. Hancock, D. E. Reichert, and M. J. Welch, Inorganic Chemistry 35 (1996) 2165.

[25] R. B. Weiss and M. C. Christian, Drugs 46 (1993) 360.

[26] B. Rosenberg, in Cisplatin, Verlag Helvetica Chimica Acta, 2006, p. 1.

[27] A. S. Abu-Surrah and M. Kettunen, Current Medicinal Chemistry 13 (2006) 1337.

[28] S. Dutta, S. Ray, and K. Nagarajan, Der Pharma Chemica 3 (2011) 263.

[29] C. A. Klein, Science 321 (2008) 1785.

[30] C. Avendaño and J. C. Menéndez, in Medicinal Chemistry of Anticancer Drugs, Elsevier, Amsterdam, 2008, p. 1.

[31] S. Nelson, L. Ferguson, and W. Denny, Cell & Chromosome 3 (2004) 2.

[32] M. J. Bissell and D. Radisky, Nature Reviews. Cancer 1 (2001) 46.

[33] C. Lengauer, L. A. Diaz, and S. Saha, Nature Reviews Drug Discovery 4 (2005) 375.

[34] P. Nygren and R. Larsson, Journal of Internal Medicine 253 (2003) 46.

[35] V. P. Torchilin, European Journal of Pharmaceutical Sciences 11, Supplement 2 (2000) S81.

[36] D. Jackman, W. Pao, G. J. Riely, J. A. Engelman, M. G. Kris, P. A. Jänne, T. Lynch, B. E. Johnson, and V. A. Miller, Journal of Clinical Oncology 28 (2010) 357.

[37] M. M. Gottesman, T. Fojo, and S. E. Bates, Nature Reviews Cancer 2 (2002) 48.

[38] D. J. Newman and G. M. Cragg, Journal of natural products 70 (2007) 461.

[39] M. S. Butler, Natural Product Reports 22 (2005) 162.

[40] A. L. Demain and P. Vaishnav, Microbial Biotechnology 4 (2011) 687.

[41] M. Tao, L. Wang, E. Wendt-Pienkowski, N. Zhang, D. Yang, U. Galm, J. M. Coughlin, Z. Xu, and B. Shen, Molecular BioSystems 6 (2009) 349.

[42] Z. Yong-su and L. Dian-dong, Chinese Journal of Antibiotics 10 (2009) 2.

[43] L. H. Einhorn and J. Donohue, The Journal of urology 167 (2002) 928.

[44] M. E. Wall and M. C. Wani, Journal of ethnopharmacology 51 (1996) 239.

[45] T. Amna, S. C. Puri, V. Verma, J. P. Sharma, R. K. Khajuria, J. Musarrat, M. Spiteller, and G. Qazi, Canadian journal of microbiology 52 (2006) 189.

[46] M. Peyrone, Justus Liebigs Annalen der Chemie 51 (1844) 1.

[47] B. Rosenberg, L. VanCamp, J. E. Trosko, and V. H. Mansour, Nature 222 (1969) 385.

[48] R. P. Perez, T. C. Hamilton, R. F. Ozols, and R. C. Young, Cancer 71 (1993) 1571.

[49] D. S. Alberts and J. K. Noel, Anti-Cancer Drugs 6 (1995) 369.

[50] Kelland, Nature Reviews. Cancer 7 (2007) 573.

[51] F. A. Cotton, G. Wilkinson, C. A. Murillo, and M. Bochmann, Advanced Inorganic Chemistry, Wiley India, 2007.

[52] L. R. Kelland, Critical Reviews in Oncology/Hematology 15 (1993) 191.

[53] Z. H. Siddik, Oncogene 22 (2003) 7265.

[54] L. R. Kelland, P. Mistry, G. Abel, S. Y. Loh, C. F. O'Neill, B. A. Murrer, and K. R. Harrap, Cancer Research 52 (1992) 3857.

[55] D. P. Gately and S. B. Howell, British journal of cancer 67 (1993) 1171.

[56] C. A. Larson, B. G. Blair, R. Safaei, and S. B. Howell, Molecular Pharmacology 75 (2009) 324.

[57] S. L. Kelley, A. Basu, B. A. Teicher, M. P. Hacker, D. H. Hamer, and J. S. Lazo, Science 241 (1988) 1813.

[58] J. Holford, P. J. Beale, F. E. Boxall, S. Y. Sharp, and L. R. Kelland, European Journal of Cancer 36 (2000) 1984.

[59] H. A. A. M. Dirven, B. van Ommen, and P. J. van Bladeren, Cancer Research 54 (1994) 6215.

[60] P. Mistry, L. R. Kelland, G. Abel, S. Sidhar, and K. R. Harrap, British journal of cancer 64 (1991) 215.

[61] S. W. Johnson, R. P. Perez, A. K. Godwin, A. T. Yeung, L. M. Handel, R. F. Ozols, and T. C. Hamilton, Biochemical Pharmacology 47 (1994) 689.

[62] S. W. Johnson, P. A. Swiggard, L. M. Handel, J. M. Brennan, A. K. Godwin, R. F. Ozols, and T. C. Hamilton, Cancer Research 54 (1994) 5911.

[63] T. L. Cornelison and E. Reed, Gynecologic Oncology 50 (1993) 147.

[64] H. H. Moon, K. W. Seo, K. Y. Yoon, Y. M. Shin, K. H. Choi, and S. H. Lee, World Journal of Gastroenterology: WJG 17 (2011) 3510.

[65] T. Taguchia and M. S. Razzaquea, Contributions To Nephrology 148 (2005) 106.

[66] J. Kovach, C. Moertel, A. Schutt, R. Reitemeier, and R. Hahn, Cancer chemotherapy reports. Part 1 57 (1973) 357.

[67] D. Higby, H. Wallace Jr, and J. Holland, Cancer chemotherapy reports. Part 1 57 (1973) 459.

[68] S. Groth, H. Nielsen, J. B. Sørensen, A. B. Christensen, A. G. Pedersen, and M. Rørth, Cancer Chemotherapy and Pharmacology 17 (1986) 191.

[69] F. Re, S. Bohm, S. Oriana, G. Battista Spatti, and F. Zunino, Cancer Chemotherapy and Pharmacology 25 (1990) 355.

[70] J. Smyth, A. Bowman, T. Perren, P. Wilkinson, R. Prescott, K. Quinn, and M. Tedeschi, Annals of oncology 8 (1997) 569.

[71] I. Kostova, Recent Patents on Anti-Cancer Drug Discovery 1 (2006) 1.

[72] R. Weiss and M. Christian, Drugs 46 (1993) 360.

[73] D. Jardim, C. Rodrigues, Y. Novis, V. Rocha, and P. Hoff, Annals of oncology 23 (2012) 1937.

[74] U. Bierbach, J. D. Roberts, and N. Farrell, Inorganic Chemistry 37 (1998) 717.

[75] S. B. Howell, C. E. Pfeifle, W. E. Wung, and R. A. Olshen, Cancer Research 43 (1983) 1426.

[76] R. Goel, S. M. Cleary, C. Horton, S. Kirmani, I. Abramson, C. Kelly, and S. B. Howell, Journal of the National Cancer Institute 81 (1989) 1552.

[77] R. F. Borch and M. E. Pleasants, Proceedings of the National Academy of Sciences 76 (1979) 6611.

[78] J. Ren, J. Diprose, J. Warren, R. M. Esnouf, L. E. Bird, S. Ikemizu, M. Slater, J. Milton, J. Balzarini, and D. I. Stuart, Journal of Biological Chemistry 275 (2000) 5633.

[79] E. S. Raper, Coordination Chemistry Reviews 165 (1997) 475.

[80] M. I. M. Wazeer, A. A. Isab, and M. Fettouhi, Polyhedron 26 (2007) 1725.

[81] J. K. Savjani and A. K. Gajjar, Pakistan Journal of Biological Sciences 14 (2011) 1076.

[82] P. D. Akrivos, Coordination Chemistry Reviews 213 (2001) 181.

[83] M. I. Wazeer and A. A. Isab, Journal of Spectroscopy 18 (2004) 113.

[84] P. Zoufalá, T. Rüffer, H. Lang, S. Ahmad, and M. Mufakkar, Analytical Sciences: X-ray Structure Analysis Online 23 (2007) x219.

[85] W. Ashraf, S. Ahmad, and A. Isab, Transition Metal Chemistry 29 (2004) 400.

[86] S. Nadeem, M. Rauf, S. Ahmad, M. Ebihara, S. Tirmizi, S. Bashir, and A. Badshah, Transition Metal Chemistry 34 (2009) 197.

[87] S. Nadeem, M. Rauf, M. Bolte, S. Ahmad, S. Tirmizi, M. Asma, and A. Hameed, Transition Metal Chemistry 35 (2010) 555.

[88] A. A. Isab, S. Ahmad, A. R. Al-Arfaj, and M. N. Akhtar, Journal of Coordination Chemistry 56 (2003) 95.

[89] S. Nawaz, S. Sadaf, M. Fettouhi, A. Fazal, and S. Ahmad, Acta Crystallographica Section E 66 (2010) m950.

[90] A. A. Isab and M. I. M. Wazeer, Journal of Coordination Chemistry 58 (2005) 529.

[91] G. D. Thorn, Canadian Journal of Chemistry 33 (1955) 1278.

[92] L. Maier, Helvetica Chimica Acta 53 (1970) 1417.

[93] K. Eichele and R. E. Wasylischen, W: Simulation Package, Version 1. 4. 4, Dalhousie University, Halifax, Canada; University of Tubingen, Tübingen, Germany, 2001.

[94] SMART APEX software (5.05) for SMART APEX Detector, Bruker Axs Inc., Madison. Wisconsin, USA.

[95] SAINT Software (5.0) for SMART APEX Detector, Bruker Axs Inc. Madison. Wisconsin, USA.

[96] G.M. Sheldrick, SADABS. Program for Empirical Absorption correction of Area detector Data. University of Gottingen, Germany, 1996.

[97] G.M. Sheldrick, SHELXTL V5.1 Software. Bruker Axs Inc., Madison. Wisconsin, USA, 1997.

[98] G.M. Sheldrick. University of Gottingen, Germany, 1997.

[99] L. Farrugia, Journal of Applied Crystallography 30 (1997) 565.

[100] J. Lin, G. Lu, L. M. Daniels, X. Wei, J. B. Sapp, and Y. Deng, Journal of Coordination Chemistry 61 (2008) 2457.

[101] R. A. Alderden, M. D. Hall, and T. W. Hambley, Journal of Chemical Education 83 (2006) 728.

[102] J. Jolley, W. I. Cross, R. G. Pritchard, C. A. McAuliffe, and K. B. Nolan, Inorganica Chimica Acta 315 (2001) 36.

[103] P. Castan and J. Laurent, Transition Metal Chemistry 5 (1980) 154.

[104] A.-M. Esmadi, Asian Journal of Chemistry 13 (2001) 128.

[105] B. H. Abdullah, M. A. Abdullah, and S. A. Al-Jibori, Asian Journal of Chemistry 19 (2007) 1334.

[106] S. Schröder and W. Preetz, Zeitschrift für anorganische und allgemeine Chemie 626 (2000) 1757.

[107] A. A. Isab, S. Ahmad, and M. Arab, Polyhedron 21 (2002) 1267.

[108] M. I. M. Wazeer, A. A. Isab, and A. El-Rayyes, Spectroscopy 18 (2004) 113.

[109] S. W. Sparks and P. D. Ellis, Journal of the American Chemical Society 108 (1986) 3215.

[110] J. D. Woollins, A. Woollins, and B. Rosenberg, Polyhedron 2 (1983) 175.

[111] L. B. Kumbhare, U. Singh, B. G. Singh, A. Wadawale, G. Kedarnath, S. S. Zade, K. I. Priyadarsini, and V. K. Jain, Inorganica Chimica Acta 374 (2011) 69.

[112] J. Lin, G. Lu, L. Daniels, X. Wei, J. Sapp, and Y. Deng, Journal of Coordination Chemistry 61 (2008) 2457.

[113] F. Allen, Acta Crystallographica Section B 58 (2002) 380.

[114] L. Fuks, N. Sadlej-Sosnowska, K. Samochocka, and W. Starosta, Journal of Molecular Structure 740 (2005) 229.

[115] P. J. M. W. L. Birker, J. Reedijk, G. C. Verschoor, and J. Jordanov, Acta Crystallographica Section B 38 (1982) 2245.

[116] Z. Popovic, D. M. Calogovic, G. Pavlovic, Z. Soldin, G. Giester, M. Rajic, and D. V. Topic, Croat. Chem. Acta 74 (2001) 359.

Vitae

Name	: Ahmed Zainelabdeen Abdalla Mustafa
Nationality	: Sudanese
Date of Birth	: 15/03/1986
Email	: ahmedzain@kfupm.edu.sa, ahmed.zine@hotmail.com.
Address	: King Fahd University of Petroleum & Minerals, P.O. Box: 8551, Postal Code: 31261, Dhahran, Saudi Arabia.
Academic Background	: B.Sc Honours degree in Chemistry (First Class) University of Khartoum, Sudan.